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(54) **Alpha-heterocycle substituted tolunitriles.**

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(73) Proprietor: **CIBA-GEIGY AG**
Klybeckstrasse 141
CH-4002 Basel(CH)

(72) Inventor: **Bowman, Robert Mathews**
6 Meadowbrook Court
Summit New Jersey 07901(US)
Inventor: **Steele, Ronald Edward**
101 Naughright Road
Long Valley New Jersey 07853(US)
Inventor: **Browne, Leslie Johnston**
Ettingerstrasse 9
CH-4147 Aesch(CH)

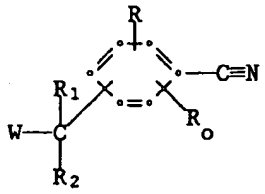
(74) Representative: **Zumstein, Fritz, Dr. et al**
Bräuhausstrasse 4
D-80331 München (DE)

Rank Xerox (UK) Business Services
(3.10/3.6/3.3.1)

Description

The invention relates to certain heterocycle-substituted tolunitriles.

Particularly the invention relates to the use of compounds of the formula I



(I)

wherein R and R_0 independently represent hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 and R_2 independently represent hydrogen, lower alkyl, (lower alkyl, aryl or aryl-lower alkyl)-thio, lower alkenyl, aryl, aryl-lower alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkyl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene, mono- or di-aryl-lower alkylidene;

R_1 and R_2 combined also represent C_4-C_6-straight chain alkylene, lower alkyl-substituted straight chain alkylene or ortho-phenylene bridged-C_2-C_4-straight chain alkylene, each forming with the carbon atom attached thereto a corresponding optionally substituted or benzo-fused 5-, 6- or 7-membered ring; W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl; or W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl substituted by lower alkyl; aryl within the above definitions represents phenyl which is unsubstituted or substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, aroyloxy, lower alkoxycarbonyloxy, N,N-di-lower alkylcarbamoyloxy, nitro, amino, halo, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, (phenyl, naphthyl, pyridyl, thienyl, indolyl or furyl)-lower alkoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, 3-phthalidoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, aroyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; 1- or 2-naphthyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, cyano or halo; a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl; or a said heterocyclic aromatic radical which is monosubstituted by lower alkyl, lower alkoxy, cyano or halo; and aroyl within the above definitions represents benzoyl which is unsubstituted or substituted by one or two of lower alkyl, lower alkoxy, halo or trifluormethyl; thienoyl, pyrroloyl or 2-, 3- or 4-pyridylcarbonyl; and radicals designated as "lower" contain up to and including 7 carbon atoms; and pharmaceutically acceptable salts thereof; for the manufacture of pharmaceutical preparations for the treatment of conditions responsive to aromatase inhibition, to certain new compounds of this kind, a process for the manufacture of the latter, pharmaceutical compositions comprising the latter and their use for the manufacture of pharmaceutical preparations for the treatment of conditions responsive to aromatase inhibition.

The compounds of the invention which possess an asymmetric carbon atom exist as racemates and the R and S enantiomers thereof. The present invention is intended to include these forms, also diastereoisomers and mixtures thereof if two or more asymmetric centers are present, as well as geometric isomers, e.g. cis and trans isomers, if a double bond is present in the molecule.

The general definitions used herein, unless denoted otherwise, have the following meanings within the scope of the present invention.

The term "lower" referred to above and hereinafter in connection with organic radicals or compounds respectively preferably defines such with up to and including 7, preferably up to and including 4 and advantageously one or two carbon atoms.

A lower alkyl group preferably contains 1-4 carbon atoms and represents for example ethyl, propyl, butyl or advantageously methyl.

A lower alkenyl group preferably contains 2-4 carbon atoms and represents for example allyl or crotyl.

A lower alkoxy group preferably contains 1-4 carbon atoms and represents for example methoxy, propoxy, isopropoxy or advantageously ethoxy.

Halogen preferably represents chlorine, but may also be bromine, fluorine or iodine.

Lower alkanoyl is preferably acetyl, propionyl, butyryl, or pivaloyl, especially acetyl.

Aroyl is benzoyl and also benzoyl substituted by one or two of lower alkyl, lower alkoxy, halogen or trifluoromethyl; aroyl is also thienoyl, pyrroloyl or 2-, 3- or 4-pyridylcarbonyl, advantageously nicotinoyl.

Lower alkanoyloxy is preferably acetoxy; and also e.g. pivaloyloxy or propionyloxy.

Aroyloxy is preferably benzoyloxy; and also e.g. benzoyloxy substituted on the benzene ring by one or two of lower alkyl, lower alkoxy, halogen or trifluoromethyl, or nicotinoyloxy.

Thienyl represents 2- or 3-thienyl, preferably 2-thienyl.

Pyridyl represents 2-, 3- or 4-pyridyl, preferably 3- or 4-pyridyl advantageously 3-pyridyl.

Furyl represents 2- or 3-furyl, preferably 3-furyl.

Indolyl represents preferably 3-indolyl.

(Phenyl, naphthyl, pyridyl, thienyl, indolyl or furyl)-lower alkoxycarbonyl is, for example, benzyloxycarbonyl or pyridylmethoxycarbonyl; lower alkanoyloxy-lower alkoxycarbonyl is, for example, pivaloyloxymethoxycarbonyl.

Aryl-lower alkyl represents preferably arylmethyl or arylethyl in which aryl represents a radical as defined above, advantageously optionally substituted phenyl as defined above.

Straight chain lower alkylidene is advantageously methylidene or ethylidene.

C_4-C_6-straight chain alkylene represents advantageously butylene or phenylene.

Ortho-phenylene bridged-C_2-C_4-straight chain alkylene represents preferably ortho-phenylene bridged CH_2CH_2.

C_3-C_6-cycloalkyl represents preferably cyclopentyl or cyclohexyl.

Pharmaceutically acceptable salts represent acid addition salts with conventional acids, for example mineral acids, e.g. hydrochloric acid, sulfuric or phosphoric acid, or organic acids, for example aliphatic or aromatic carboxylic or sulfonic acids, e.g. acetic, propionic, succinic, glycolic, lactic, malic, tartaric, citric, ascorbic, maleic, fumaric, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, pamoic, gluconic, nicotinic, methanesulfonic, ethanesulfonic, halobenzenesulfonic, toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; also amino acids, such as arginine and lysine. For compounds of the invention having acidic groups, for example a free carboxy group, pharmaceutically acceptable salts also represent metal or ammonium salts, such as alkali metal or alkaline earth metal salts, e.g. sodium, potassium, magnesium or calcium salts, as well as ammonium salts, which are formed with ammonia or suitable organic amines.

The compounds of formula I have valuable pharmacological properties. For example, they are useful as inhibitors of aromatase activity and inhibitors of estrogen biosynthesis in mammals, and for treating conditions responsive thereto. These compounds inhibit the metabolic conversion of androgens to estrogens in mammals. Thus, these compounds are useful e.g. in the treatment of gynecomastia, i.e. male breast development, by inhibiting the aromatization of steroids in males susceptible to this condition. Moreover, the compounds of the invention are useful e.g. in the treatment of estrogen dependent diseases in females, for example estrogen dependent female breast cancer, especially in postmenopausal females, by inhibiting estrogen biosynthesis.

These effects are demonstrable in in vitro assay tests or in vivo animal tests using advantageously mammals, e.g. guinea pigs, mice, rats, cats, dogs, or monkeys. The applied dosage may range between about 0.001 and 30 mg/kg, preferably between about 0.001 to 5 mg/kg.

The in vitro inhibition of aromatase activity of the compounds of formula I can be demonstrated e.g. as follows: A microsomal fraction is prepared from human placenta by the method essentially as described by Thompson and Siiteri, J. Biol. Chem. 249, 5364 (1974). The microsomal preparation so obtained is lyophilized and stored at -40 °C. The assay is conducted substantially as described by Thompson and Siiteri. IC_{50} values can be determined graphically as the concentration of test compound at which the aromatization of androstenedione to estrone is reduced to 50% of control value. The compounds of formulae I, IV and VI are effective at concentrations of about 10^{-9} M or above.

The in vivo inhibition of aromatase activity of the compounds of formula I can be demonstrated e.g. by measuring the inhibition of estrogen synthesis in rats. The inhibition of estrogen synthesis, indicative of aromatase inhibition, is calculated from the ovarian estrogen content in treated as compared to control animals. The compounds of the invention inhibit estrogen synthesis at a dose of about 3 µg/kg p.o. or above in the female rat.

The in vivo inhibition of aromatase activity can be also assessed e.g. as follows: Androstenedione (30 mg/kg subcutaneously) alone and together with the aromatase inhibitor under investigation (orally or subcutaneously) is administered to immature female rats once daily for 4 days. After the fourth application, the rats are sacrificed and their uteri removed and weighed. The inhibition of aromatase can be assessed by determining the extent to which the uterine hypertrophy elicited by androstenedione alone is suppressed by co-administration of the aromatase inhibitor.

The antitumor activity, especially in estrogen-dependent tumors, can be demonstrated in vivo e.g. in dimethylbenzanthracene (DMBA)-induced mammary tumors in female Sprague-Dawley rats [see Proc. Soc. Exp. Biol. Med. 160, 296-301 (1979)]. Compounds of the formula I cause regression of existing tumors and

suppress the appearance of new tumors at daily doses of about 0.1 mg/kg p.o. or above.

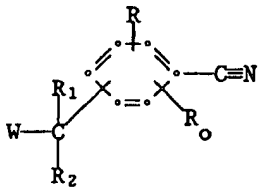
Furthermore, the compounds of the formula I are essentially devoid of cholesterol side chain cleavage inhibitory activity and do not induce adrenal hypertrophy at effective aromatase inhibitory doses.

Due to their pharmacological properties as selective aromatase inhibitors, the compounds of the formula I are useful for the inhibition of estrogen biosynthesis in mammals and the treatment of estrogen dependent disorders responsive thereto, such as mammary tumors (breast carcinoma), endometriosis, premature labor and endometrial tumors in females, as well as gynecomastia in males.

Preferred is the use of the compounds of formula I wherein R and R_0 represent independently hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl or lower alkenyl; R_2 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl, (lower alkyl, aryl or aryl-lower alkyl)-thio or lower alkenyl; or R_1 and R_2 combined represent lower alkylidene or C_4-C_6-alkylene; W has meaning given above; and aryl within the above definitions represents phenyl or phenyl substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, sulfamoyl, N-lower-alkylsulfamoyl or N,N-di-lower alkylsulfamoyl; or aryl within the above definitions also represents a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl, or said heterocyclic radical monosubstituted by lower alkyl, lower alkoxy, cyano or halogen; or a pharmaceutically acceptable salt thereof.

Particularly preferred is the use of said compounds of formula I wherein R_1 represents hydrogen; and W, R, R_0, R_2 as well as R_1 and R_2 combined have meaning as defined in the last paragraph.

Furthermore, the invention relates to the compounds of the formula I



(I)

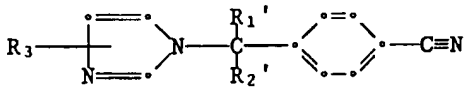
wherein R and R_0 independently represent hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 represents hydrogen; R_2 represents hydrogen, lower alkyl, lower alkenyl, aryl, aryl-lower alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkyl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene, or mono- or di-aryl-lower alkylidene; R_1 and R_2 combined also represent C_4-C_6-straight chain alkylene, lower alkyl-substituted straight chain alkylene or ortho-phenylene bridged-C_2-C_4-straight chain alkylene, to form with the carbon atom attached thereto a corresponding optionally substituted or benzo-fused 5-, 6- or 7-membered ring; W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl; or W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl substituted by lower alkyl; and aryl within the above definitions represents phenyl which is unsubstituted or substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, aroyloxy, lower alkoxycarbonyloxy, N,N-di-lower alkylcarbamoyloxy, nitro, amino, halo, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, (phenyl, naphthyl, pyridyl, thienyl, indolyl or furyl)-lower alkoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, 3-phthalidoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, aroyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; 1- or 2-naphthyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, cyano or halo; a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl; or a said heterocyclic aromatic radical which is monosubstituted by lower alkyl, lower alkoxy, cyano or halo;
and aroyl within the above definitions represents benzoyl which is unsubstituted or substituted by one or two of lower alkyl, lower alkoxy, halo or trifluormethyl; thienoyl, pyrroloyl or 2-, 3- or 4-pyridylcarbonyl;
and radicals designated as "lower" contain up to and including 7 carbon atoms; and pharmaceutically acceptable salts thereof.

Especially preferred are the compounds of the formula I, wherein R and R_0 represent hydrogen; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene ring; R_1 represents hydrogen; R_2 represents hydrogen, lower alkyl, aryl or aryl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene or di-aryl-lower alkylidene; R_1 and R_2

combined also represent C_4-C_6-straight chain alkylene or ortho-phenylene bridged-C_2-C_4-straight chain alkylene, to form with the carbon atom attached thereto a corresponding optionally benzo-fused 5-, 6- or 7-membered ring; W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl, 3-pyridyl, or 1-imidazolyl substituted by lower alkyl; and aryl within the above definitions represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, hydroxy, halogen, trifluoromethyl or cyano; thienyl or pyridyl; and pharmaceutically acceptable salts thereof.

Also preferred are the compounds of formula I, wherein R and R_0 independently represent hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 represents hydrogen; R_2 represents hydrogen, lower alkyl, lower alkenyl, aryl, or aryl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene or C_4-C_6-alkylene; W represents 1-imidazolyl or 1-imidazolyl substituted by lower alkyl; and aryl within the above definitions represents phenyl or phenyl substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halogen, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl or N,N-di-lower alkylsulfamoyl; or aryl within the above definitions also represents a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl, or a said heterocyclic radical mono-substituted by lower alkyl, lower alkoxy, cyano or halogen; and pharmaceutically acceptable salts thereof.

Further preferred are the compounds of formula II



(II)

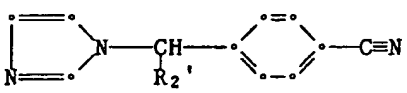
wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, pyridyl, thienyl or benzyl; or R_2' represents phenyl or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halogen, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene or diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

Particularly preferred are the compounds of formula II wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, pyridyl, benzyl or phenyl; or R_2' represents benzyl or phenyl, each monosubstituted on phenyl by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen, nitro, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

Preferred in turn are the compounds of formula II wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl, each monosubstituted on phenyl by cyano, halogen, lower alkoxy, lower alkyl or trifluoromethyl; R_3 represents hydrogen or lower alkyl at the 4- or 5-position; and pharmaceutically acceptable salts thereof.

Particularly preferred are the compounds of formula II wherein R_2' represents unsubstituted or monosubstituted phenyl or benzyl, or pyridyl, as defined hereinabove.

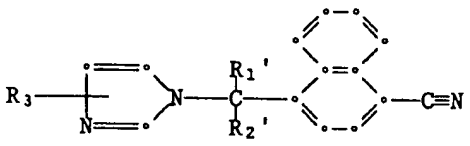
Most preferred are the compounds of formula III



(III)

wherein R_2' represents 3-pyridyl, p-cyanobenzyl or p-cyanophenyl; and pharmaceutically acceptable salts thereof.

A particular embodiment of the invention relates to the compounds of formula I wherein R and R_0 are located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring, said embodiment relating to the naphthonitriles of formula IV



(IV)

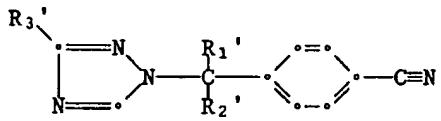
wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, lower alkylthio, phenyl-lower alkylthio, phenylthio, pyridyl, thienyl or benzyl; or R_2' represents phenyl, phenyl-lower alkylthio, phenylthio or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halogen, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene, diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

Particularly preferred are the compounds of formula IV wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, pyridyl; or R_2' represents benzyl or phenyl, each unsubstituted or monosubstituted on phenyl by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen, nitro, trifluoromethyl, lower alkanoyl, aroyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

Preferred in turn are the compounds of formula IV wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl, each monosubstituted on phenyl by cyano, halogen, lower alkoxy, lower alkyl or trifluoromethyl; R_3 represents hydrogen or lower alkyl at the 4- or 5-position; and pharmaceutically acceptable salts thereof.

Most preferred are the compounds of formula IV wherein R_1' and R_3 represent hydrogen; R_2' represents 3-pyridyl, p-cyanobenzyl or p-cyanophenyl; and pharmaceutically acceptable salts thereof.

Another specific preferred embodiment of the invention relates to compounds of formula I wherein W represents 1-(1,2,4)-triazolyl or 1-(1,2,4)-triazolyl substituted by lower alkyl, namely the compounds of formula V



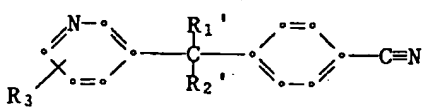
(V)

wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, pyridyl, thienyl or benzyl; or R_2' represents phenyl or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halogen, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene or diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3' represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

Preferred in turn are the compounds of formula V wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl, each monosubstituted on phenyl by cyano, halogen, lower alkoxy, lower alkyl or trifluoromethyl; R_3' represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

Most preferred are the compounds of formula V wherein R_1' and R_3' represent hydrogen; R_2' represents 3-pyridyl, p-cyanobenzyl or p-cyanophenyl; and pharmaceutically acceptable salts thereof.

A further specific embodiment of the invention relates to compounds of the formula I wherein W represents a 3-pyridyl group, namely the compounds of formula VI



(VI)

wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, lower alkylthio, phenyl-lower alkylthio, phenylthio, pyridyl, thienyl, benzyl; or R_2' represents phenyl, phenyl-lower alkylthio, phenylthio or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halogen, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene or diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_5 straight chain alkylene; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

Particularly preferred are the compounds of formula VI wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, pyridyl; or R_2' represents benzyl or phenyl each unsubstituted or monosubstituted on phenyl by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halogen, nitro, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

Preferred in turn are the compounds of formula VI wherein R_1' and R_3 represent hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl each substituted on phenyl by cyano, halogen, lower alkoxy, lower alkyl or trifluoromethyl; and pharmaceutically acceptable salts thereof.

Most preferred are the compounds of formula VI wherein R_1' and R_3 represent hydrogen; R_2' represents 3- or 4-pyridyl, p-cyanobenzyl or p-cyanophenyl; and pharmaceutically acceptable salts thereof.

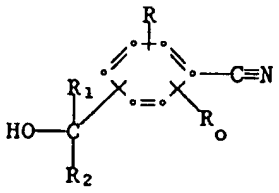
Above all are preferred the compounds of formula I described in the examples and pharmaceutically acceptable salts thereof.

The compounds of formula I or II-VI may be prepared as follows:

a) for compounds of formula I wherein W represents 1-imidazolyl or 1-triazolyl each optionally substituted by lower alkyl, condensing a compound of the formula VII

W'-H (VII)

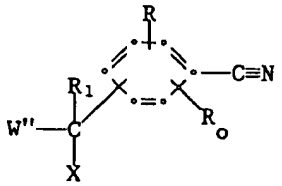
wherein W' represents 1-imidazolyl or 1-triazolyl each optionally substituted by lower alkyl, or an N-protected derivative thereof, with a reactive esterified derivative of a compound of the formula VIII



(VIII)

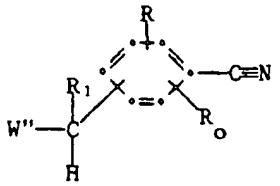
wherein R, R_0, R_1 and R_2 have meaning as defined herein for formula I;

b) for compounds wherein W represents 3-pyridyl optionally substituted by lower alkyl, dehalogenating a compound of the formula IX



(IX)

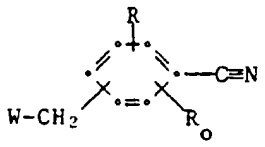
wherein W" represents 3-pyridyl optionally substituted by lower alkyl, X represents halogen, preferably chloro, R and R_0 have meaning as defined herein for compounds of formula I and R_1 has meaning as defined herein for formula I; and if required reacting the resulting product of formula X



(X)

with a reactive derivative of the radical R_2 using process c) below;

c) condensing under basic conditions a compound of the formula XI

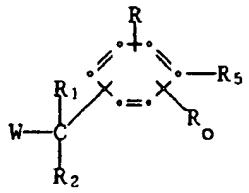


(XI)

(being a compound of formula I wherein R_1 and R_2 represent hydrogen)

wherein R, R_o and W have meaning as defined herein for formula I, with a reactive functional derivative of a radical R_1 or R_2 (R_1 or R_2 not representing hydrogen), so as to obtain a compound of formula I wherein only one of R_1 and R_2 represents hydrogen; or similarly condensing a compound of formula I so obtained with a reactive functional derivative of a radical R_1 or R_2 (R_1 or R_2 not representing hydrogen) to obtain a compound of formula I wherein neither R_1 nor R_2 represents hydrogen; or condensing a compound of the formula XI with a reactive bifunctional derivative of R_1 and R_2 combined representing C_4-C_6 straight alkylene, lower alkyl substituted C_4-C_6 straight chain alkylene or 1,2-phenylene-bridged-C_2-C_4 straight chain alkylene to obtain a corresponding compound of formula I;

d) converting R_5 to cyano in a compound of the formula XII



(XII)

wherein W, R, R_o, R_1 and R_2 have meaning as defined above and R_5 represents a group or radical that can be converted to the cyano group;

and/or converting a compound of formula I into another compound of formula I; and/or converting a free compound into a salt, and/or converting a salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates into the single isomers or racemates and/or resolving a racemate into the optical isomers.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as carboxy, amino (including ring NH) and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected carboxy, amino and hydroxy groups are those that can be converted under mild conditions into free carboxy, amino and hydroxy groups without the molecular framework being destroyed or other undesired side reactions taking place. The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components and under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (carboxy group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part, and the reaction conditions. Well-known protecting groups that meet these conditions and their introduction and removal are described, for example, in J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York, 1973; T.W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York, 1984.

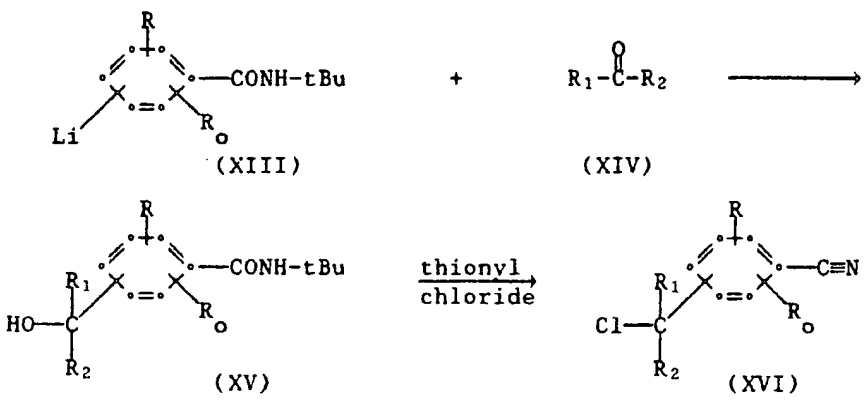
Relating to the above processes, a reactive functional derivative of the radicals R_1 and R_2 represents said radicals substituted by a leaving group, preferably by lower alkyl- or aryl-sulfonyloxy, e.g. mesyloxy or toluenesulfonyloxy, or by halogen, e.g. fluoro, chloro, bromo or iodo. Similarly, a reactive esterified derivative of an alcohol, e.g. of a compound of formula VIII, represents said alcohol esterified in the form of a leaving group, e.g. lower alkyl- or aryl-sulfonyloxy, such as mesyloxy or toluenesulfonyloxy, or halogen, such as chloro, bromo or iodo.

Protecting groups for the imidazolyl nitrogen are preferably tri-lower alkylsilyl, e.g. trimethylsilyl, lower alkanoyl, e.g. acetyl, di-lower alkylcarbamoyl such as dimethylcarbamoyl, or triarylmethyl, e.g. triphenylmethyl.

The condensation according to process (a) is carried out according to N-alkylation procedures well-known in the art, either as such or in the presence of a base such as triethylamine or pyridine in an inert solvent, e.g. dichloromethane, at room temperature or near the boiling point of the solvent used.

A N-protected derivative of formula VII is particularly used, when a compound of formula I wherein W is 1-imidazolyl or lower-alkyl-substituted 1-imidazolyl is prepared. In the case of protected imidazolyl, alkylation occurs on the second unprotected nitrogen to first form a quaternary compound which is advantageously simultaneously deprotected in situ prior to the isolation of the product. The imidazole and triazole starting materials of formula VII are either known or are prepared according to methods known in the art.

The nitrile substituted starting materials representing reactive esterified derivatives of the carbinols of formula VIII are also either known or are prepared e.g. as illustrated below and in the examples herein. For example, the halo substituted starting materials can be advantageously prepared using the following illustrative sequence of reactions (tBu ≙ tert-butyl) using appropriate reaction conditions known in the art and illustrated in the examples.



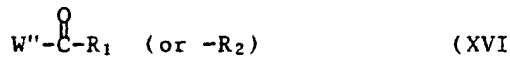
The starting materials of formula XIV represent appropriate aldehydes or ketones in which R_1 and R_2 correspond to relevant definitions in formula I.

For compounds of formula I wherein R_1 represents hydrogen and R_2 represents cyanophenyl, the intermediate corresponding to formula XV can be advantageously prepared by reacting the lithium organometallic reagent of formula XIII with ethyl formate (instead of a compound of formula XIV) in the above sequence of reactions.

It should also be noted that in the above intermediate XIII, the CONH-tBu substituent may be replaced by cyano or any other grouping suitable for the condensation and known in the art to be convertible into cyano. Such groupings are included under process (d) (R_5 in formula XII).

The dehalogenation under process (b) for the preparation of the compounds of formula I wherein W represents pyridyl optionally substituted by lower alkyl can be achieved advantageously with zinc in acetic acid. Other suitable reagents include tributyl tin hydride or aluminium amalgam.

The starting halides of formula IX can be prepared from an alcohol with a halogenating agent, e.g. thionyl chloride as described under process (a). The alcohol can in turn be prepared by condensation of a compound of formula XIII or the like with an appropriate aldehyde or ketone of the formula XVII



in which R_1 and R_2 correspond to relevant definitions for R_1 and R_2 in formula I and W" represents 3-pyridyl.

The condensation according to process (c) is carried out according to procedures generally known in the art for displacement e.g. of a halo, lower alkyl- or aryl-sulfonyloxy leaving group, e.g. by first forming a carbanion in the presence of a strong base such as lithium diisopropylamide, an alkali metal hydride, an alkali metal alkoxide such as potassium t-butoxide, or a strongly basic tertiary amine such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), preferably in an inert atomosphere, for example under a nitrogen atmosphere, and in a polar solvent such as dimethylformamide.

For compounds of formula I wherein R_1 and/or R_2 represents p-cyanophenyl a suitable reactive derivative is p-fluorobenzonitrile. For compounds wherein R_1 or R_2 represents (lower alkyl, aryl or aryl-lower alkyl)-thio, suitable reactive derivatives are the disulfides corresponding thereto, such as diphenyl disulfide or dimethyl disulfide.

Process (d) is carried out according to known methods for the introduction of a nitrile group.

A group or radical R_5 in a compound formula XII which can be converted into the CON group, is, for example, hydrogen, esterified hydroxy, for example halo, especially chloro, bromo, or iodo, or a sulfonyloxy group, for example p-toluenesulfonyloxy, benzenesulfonyloxy or mesyloxy, sulfo, amino, carboxy, carboxy in the form of a functional derivative, for example carbamoyl, lower alkylcarbamoyl, for example t-butyl-carbamoyl, or haloformyl, for example chloro- or bromoformyl, formyl, a formyl group in the form of a functional derivative, for example hydroxyiminomethyl, or a halomagnesium group, for example iodo-, bromo- or chloromagnesium.

Compounds of the formula I (or II-VI) can be obtained, for example, by carrying out the following conversions:

The conversion of a compound of the formula XII wherein R_5 is hydrogen, to the corresponding nitrile of the formula I is performed e.g. according to the known method of C. Friedel, F.M. Crafts and P. Karrer by reacting with cyanogen chloride (ClCN) or cyanogen bromide or according to the method of J. Houben and W. Fisher, by reacting with e.g. trichloroacetonitrile. Advantageously, the standard catalyst aluminium chloride is used in these reactions and hydrogen chloride or hydrogen bromide is released which can be removed from the reaction mixture after addition of a base, preferably an amine, for example triethylamine or pyridine.

The conversion of a compound of the formula XII wherein R_5 is halo, for example, chloro, bromo or iodo, to a corresponding nitrile of the formula I is performed by using e.g. a cyanide salt, especially sodium or potassium cyanide or, preferably, copper(I) cyanide. Preferred solvents for this reaction are pyridine, quinoline, dimethylformamide, 1-methyl-2-pyrrolidinone and hexamethylphosphoric triamide. High temperatures, especially reflux temperatures of the reaction mixture are preferred.

The conversion of a compound of the formula XII wherein R_5 is a sulfonyloxy group, for example p-toluenesulfonyloxy, benzenesulfonyloxy or mesyloxy, to a nitrile of the formula I is performed e.g. by reaction with an alkali metal cyanide, preferably sodium or potassium cyanide. High temperatures, expecially the reflux temperature of the reaction mixture, are preferred.

The conversion of a compound of the formula XII wherein R_5 is amino, to a nitrile of the formula I proceeds over several steps. First, a diazonium salt is formed e.g. by reaction of the amino compound with an alkali metal nitrite preferably potassium nitrite. The diazonium salt can be reacted using the well-known Sandmeyer reaction in situ e.g. with cuprous cyanide or a cyanide complex preferably potassium cuproammonium cyanide, or with catalytic amounts of freshly precipitated copper powder in the presence of an alkali metal cyanide, for example sodium or potassium cyanide.

The conversion of a compound of formula XII wherein R_5 is carboxy to a nitrile of formula I can be carried out e.g. by reaction with chlorosulfonylisocyanate in e.g. dimethylformamide according to the method of R. Graf, Angew. Chem. 80, 183 (1968).

The conversion of a compound of the formula XII wherein R_5 is a carboxy group in the form of a functional derivative, for example carbamoyl, lower alkylcarbamoyl, advantageously t-butylcarbamoyl, to a nitrile of the formula I can be carried out e.g. with a strong dehydrating agent, such as phosphorous pentoxide, phosphoryl chloride, thionyl chloride, phosgene or oxalyl chloride. The dehydration can be preferably carried out in the presence of a suitable base. A suitable base is, for example, an amine, for example a tertiary amine, for example tri-lower alkylamine, for example trimethylamine, triethylamine or ethyl diisopropylamine, or N,N-di-lower alkylaniline, for example N,N-dimethylaniline, or a cyclic tertiary amine, for example a N-lower alkylated morpholine, for example N-methylmorpholine, or is, for example, a base of the pyridine type, for example pyridine or quinoline.

The conversion of a compound of formula XII wherein R_5 is formyl to a nitrile of formula I is carried out e.g. by converting the formyl group to a reactive functional derivative, for example a hydroxyiminomethyl

group, and converting this group to cyano by a dehydrating agent. A suitable dehydrating agent is one of the inorganic dehydrating agents mentioned above, for example phosphorous pentachloride, or, preferably, the anhydride of an organic acid, for example the anhydride of a lower alkane carboxylic acid, for example acetic acid anhydride. The conversion of the formyl group to hydroxyiminomethyl is carried out by reaction of a compound of formula XII wherein R_5 is formyl, e.g. with an acid addition salt of hydroxylamine, preferably the hydrochloride.

A compound of the formula XII wherein R_5 is formyl can also be converted directly to a corresponding nitrile of the formula I e.g. by reaction with O,N-bis(trifluoroacetyl)-hydroxylamine in the presence of a base, for example pyridine, according to the method of D. T. Mowry, Chem. Rev. 42, 251 (1948).

The conversion of a compound of the formula XII wherein R_5 is a halomagnesium group, for example, iodo-, bromo-, or chloromagnesium, to a corresponding nitrile of the formula I is performed e.g. by reacting the magnesium halide with cyanogen halide or dicyanogen. The "Grignard" reagent, wherein R_5 is a halomagnesium group, is prepared in a conventional manner, for example by reacting a compound of the formula XII wherein R_5 is halo, for example chloro, bromo or iodo, with magnesium, e.g. in dry ether.

The compounds of the invention obtained by the above-cited processes can be converted into other compounds of the invention of formula I according to methodology known in the art and as illustrated herein.

Compounds of formula I, substituted by e.g. an acyloxy group, such as lower alkanoyloxy or aroyloxy, may be converted to compounds of formula I substituted by hydroxy, by hydrolysis with e.g. aqueous acid such as hydrochloric acid, or with aqueous alkali, such as lithium or sodium hydroxide.

Conversely, the conversion of compounds of formula I substituted by hydroxy to compounds of formula I substituted by acyloxy, such as alkanoyloxy or aroyloxy, may be carried out by condensation with a corresponding carboxylic acid, or a reactive functional derivative thereof, according to acylation (esterification) procedures well-known to the art.

The conversion of the compounds of formula I substituted by an etherified hydroxy group, e.g. lower alkoxy, to the compounds of formula I substituted by a hydroxy group is carried out by methods well-known in the art, e.g., with a mineral acid, such as hydriodic acid or, advantageously for compounds wherein lower alkoxy is methoxy, with e.g. boron tribromide in methylene chloride or with sodium or lithium diphenylphosphide in tetrahydrofuran.

The compounds of formula I wherein R_1 and R_2 represent hydrogen, i.e. the compounds of formula XI, may be converted to the compounds of formula I wherein R_1 and R_2 combined represent lower alkylidene, mono- or diaryl-lower alkylidene by reacting said compounds of formula XI with an appropriate aldehyde or ketone in the presence of a strong base, e.g. lithium diisopropylamide, and, if required, treating the resulting alcohols with a dehydrating agent, such as thionyl chloride.

Furthermore, the compounds of formula I wherein at least one of R_1 and R_2 represents hydrogen are converted to other compounds of formula I as described above under process c).

Unless stated otherwise, the above reactions are preferably carried out in an inert, preferably anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example a formamide, for example dimethylformamide, a halogenated hydrocarbon, for example methylene chloride or chloroform, a ketone, for example acetone, a cyclic ether, for example tetrahydrofuran, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or in mixtures thereof, optionally at reduced or elevated temperature, for example in a temperature range from approximately -50 °C to approximately +150 °C, preferably from room temperature to the boiling temperature of the reaction mixture and optionally under inert gas atmosphere, for example nitrogen atmosphere, and preferably at atmospheric pressure.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions or in which the reaction components are used in the form of their salts or optically pure antipodes. Whenever desirable, the above processes are carried out after first suitably protecting any potentially interfering reactive functional groups, as illustrated above and in the examples herein.

Advantageously, those starting materials should be used in said reactions, that lead to the formation of those compounds indicated above as being preferred.

The invention also relates to novel starting materials and processes for their manufacture.

Depending on the choice of starting materials and methods, the new compounds may be in the form of one of the possible isomers or mixtures thereof, for example, as pure geometric isomers (cis or trans), as pure optical isomers (as antipodes), or as mixtures of optical isomers such as racemates, or as mixtures of geometric isomers.

In case geometric or diastereomeric mixtures of the above compounds of intermediates are obtained, these can be separated into the single racemic or optically active isomers by methods in themselves known, e.g. by fractional distillation, crystallization and/or chromatography.

The racemic products or basic intermediates can be resolved into the optical antipodes, for example, by separation of diastereomeric salts thereof, e.g., by the fractional crystallization of d- or l-(tartrate, dibenzoyltartrate, mandelate or camphorsulfonate) salts.

Any acidic intermediates or products can be resolved by separation of e.g. the d- and l-(alpha-methylbenzylamine, cinchonidine, cinchonine, quinine, ephedrine, dehydroabietylamine, brucine or strychnine)-salts of any compounds having an acidic salt-forming group.

Advantageously, the more active of the antipodes of the compounds of this invention is isolated.

Finally, the compounds of the invention are either obtained in the free form, or as a salt thereof. Any resulting base can be converted into a corresponding acid addition salt, preferably with the use of a pharmaceutically acceptable acid or anion exchange preparation, or resulting salt can be converted into the corresponding free bases, for example, with the use of a stronger base, such as a metal or ammonium hydroxide, or any basic salt, e.g., an alkali metal hydroxide or carbonate, or a cation exchange preparation. These or other salts, for example, the picrates, can also be used for purification of the bases obtained; the bases are converted into salts. In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a compound is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The compounds, including their salts, may also be obtained in the form of their hydrates, or include other solvents used for the crystallization.

The pharmaceutical compositions according to the invention are those suitable for enteral, such as oral or rectal, transdermal and parenteral administration to mammals, including man, comprising an effective amount of a pharmacologically active compound of formula I, or II, III, IV, V or VI or a pharmacologically acceptable salt thereof, alone or in combination with one or more pharmaceutically acceptable carriers.

The pharmacologically active compounds of the invention are useful in the manufacture of pharmaceutical compositions comprising an effective amount thereof in conjunction or admixture with excipients or carriers suitable for either enteral or parenteral application. Preferred are tablets and gelatin capsules comprising the active ingredient together with a) diluents, e.g. lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine; b) lubricants, e.g. silica, talcum, stearic acid, its magnesium or calcium salts and/or polyethyleneglycol; for tablets also c) binders, e.g. magnesium aluminium silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired, d) disintegrants, e.g. starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or e) e.g. absorbents, colorants, flavors and sweeteners. Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In addition, the compositions may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain preferably about 1 to 50% of the active ingredient.

The dosage of active compound administered is dependent on the species of warm-blooded animal (mammal), the body weight, age and individual condition, and on the form of administration. A unit dosage for a mammal of about 50 to 70 kg may contain between about 5 and 100 mg of the active ingredient.

Suitable formulations for transdermal application include an effective amount of a compound of formula I or II-VI with carrier. Advantageous carriers include absorbable pharmaceutically acceptable solvents to assist passage through the skin of the host. Characteristically, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound, optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

The following examples are intended to illustrate the invention. Temperatures are given in degrees Centigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 20 and 130 mbar. The structure of final products, intermediates and starting materials is confirmed by analytical methods, e.g. microanalysis and spectroscopic characteristics (e.g. MS, IR, NMR). The following abbreviations are used: HCl = hydrochloric acid, THF = tetrahydrofuran, DMF = dimethylformamide.

Example 1:

a) A solution of alpha-bromo-4-tolunitrile (86.6 g) in dichloromethane (1000 ml) is mixed with imidazole (68.0 g). The mixture is stirred at ambient temperature for 15 h and then diluted with water (1000 ml). Any undissolved solid is removed by filtration and the separated organic solution is then repeatedly washed with water (5 x 200 ml) to remove excess imidazole, and then dried ($MgSO_4$). The crude product obtained upon evaporation of the solvent can be purified by trituration with cold diethyl ether (200 ml) to obtain 4-(1-imidazolylmethyl)-benzonitrile, m.p. 99-101°; HCl salt, m.p. 142-144°.

Similarly prepared are:

b) 2-(1-imidazolylmethyl)-benzonitrile hydrochloride, m.p. 176-177°;

c) 4-(1-imidazolylmethyl)-1-naphthonitrile hydrochloride, m.p. 210-212° (dec.).

Example 2:

a) A suspension of potassium tert-butoxide (61.6 g) in DMF (500 ml) is stirred and cooled to -10° (ice-salt bath), and a solution of 4-(1-imidazolylmethyl)-benzonitrile (45.6 g) in DMF (250 ml) is added so that the reaction temperature remains below 0°. The resulting solution is stirred at 0° for 0.5 h and then a solution of 4-fluorobenzonitrile (38.3 g) in DMF (100 ml) is added while keeping reaction temperature below 5°. After 0.75 h, the reaction mixture is neutralized to pH 7 by addition of sufficient 3N HCl and the bulk of the solvents are then removed under reduced pressure. The residue is diluted with water (500 ml) and the crude product is extracted into ethyl acetate (3 x 200 ml). The combined extracts are then extracted with 3N HCl (3 x 150 ml) and, after washing the latter acid extracts with ethyl acetate (100 ml), the solution is made basic (pH 8) with 6N ammonium hydroxide and the product is again extracted into ethyl acetate (3 x 150 ml). The combined extracts are dried ($MgSO_4$), decolorized by treatment with charcoal, and then evaporated to give crude 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile as an oil. This material is dissolved in isopropanol (250 ml) and the warm solution is stirred with succinic acid (14.4 g). Upon dilution with diethyl ether (100 ml) and stirring at ambient temperature, the hemisuccinate salt separates. The salt is filtered off, washed with a little cold isopropanol and then air-dried to afford 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile hemisuccinate, m.p. 149-150°. The hemifumarate salt has m.p. 157-158°.

Similarly prepared are:

b) 4-[alpha-(2-cyanophenyl)-1-imidazolylmethyl]-benzonitrile, IR(CN) 2240 cm^{-1}, M/e 384; HCl salt (hygroscopic), m.p. 90° (dec.);

c) 4-[alpha-(4-trifluoromethylphenyl)-1-imidazolylmethyl]-benzonitrile, IR(CN) 2232 cm^{-1}, M/e 327; HCl salt (hygroscopic), m.p. 100° (dec.).

Example 3:

A solution of 4-(alpha-chloro-4'-cyanobenzyl)-benzonitrile (20.2 g) and imidazole (16.3 g) in DMF (130 ml) is stirred and heated at 160° for 2 h. The reaction is cooled, diluted with water (800 ml) and extracted into ethyl acetate (3 x 150 ml). The remainder of the work-up is carried out in the manner described in Example 2 to yield 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile hemisuccinate, m.p. 148-150°.

The starting material, 4-(alpha-chloro-4'-cyanobenzyl)-benzonitrile is prepared as follows:

A solution of N-tert-butyl-4-bromobenzamide (37.2 g) in anhydrous THF (1000 ml) is stirred under an atmosphere of N_2 and cooled to -60°. A solution of n-butyl lithium (125 ml, 2.4 M in hexane, 0.300 mole) is then added during 40 min and the resulting suspension is stirred for a further 40 min at -60°. A solution of ethyl formate (5.3 g) in anhydrous THF (50 ml) is then added dropwise during 10 min and the reaction is allowed to proceed at -60° for 2 h. The reaction is then quenched by the addition of saturated aqueous ammonium chloride (200 ml) and after allowing the mixture to reach room temperature, diethyl ether (300 ml) is added and the layers are separated. The ethereal solution is washed with water (2 x 100 ml) and brine (100 ml) and dried ($MgSO_4$). The solvent is evaporated and the residue is triturated with diethyl ether (150 ml) to afford the bis-(4-N-tert-butylcarbamoylphenyl)methanol, m.p. 200-202°.

Bis-(4-N-tert-butylcarbamoylphenyl)-methanol (17.6 g) is suspended in thionyl chloride (140 ml) and the mixture is stirred at reflux for 6 h. The solvent is evaporated and the residue is taken up in toluene (100 ml) and the solvent is evaporated. The latter procedure is repeated once more to afford the 4-(alpha-chloro-4'-cyanobenzyl)-benzonitrile as an oil which is used directly; NMR(CH methine) 3.85 ppm.

Example 4:

Imidazole (9.4 g) and 4-(alpha-chloro-4'-cyanobenzyl)-benzonitrile (11.6 g) are intimately mixed and heated together in an oil bath at 110-120° for 15 h. The reaction mixture is diluted with water (200 ml) and extracted with ethyl acetate (3 x 75 ml). The remainder of the work-up is carried out as described in Example 2, yielding 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile. The crude product is treated with an equivalent amount of fumaric acid in warm isopropanol to yield 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile hemifumarate, m.p. 156-157°.

Example 5:

The following compounds are prepared according to the methods described in previous examples 3 and 4 using the appropriate starting materials.

a) 2-[alpha-(4-bromophenyl)-1-imidazolylmethyl]-benzonitrile, M/e 337;

b) 4-[alpha-(4-chlorophenyl)-1-imidazolylmethyl]-benzonitrile; M/e 293; hydrochloride salt, m.p. 90° (dec.);

c) 4-[alpha-(4-methoxyphenyl)-1-imidazolylmethyl]-benzonitrile, IR(CN) 2235 cm^{-1}, M/e 289; hydrochloride salt (hygroscopic), m.p. 90° (dec.);

d) 4-[alpha-(2-methoxyphenyl)-1-imidazolylmethyl]-benzonitrile, IR(CN) 2234 cm^{-1}, M/e 289; hydrochloride salt (hygroscopic), m.p. 95° (dec.);

e) 4-[alpha-(3-pyridyl)-1-imidazolylmethyl]-benzonitrile, IR(CN) 2237 cm^{-1}, M/e 260; dihydrochloride salt (hygroscopic), m.p. 150°;

f) 4-[alpha-(2-thienyl)-1-imidazolylmethyl]-benzonitrile, IR(CN) 2237 cm^{-1}; M/e 265; hydrochloride salt, m.p. 65° (dec.);

g) 4-[alpha-(3-thienyl)-1-imidazolylmethyl]-benzonitrile, IR(CN) 2240 cm^{-1}, M/e 265; hydrochloride salt, m.p. 70° (dec.);

h) 4-(alpha-phenyl-1-imidazolylmethyl)-benzonitrile; M/e 259; hydrochloride salt (hygroscopic), m.p. 90° (dec.);

i) 4-[alpha-(4-tolyl)-1-imidazolylmethyl]-benzonitrile; M/e 273; hydrochloride salt (hygroscopic), m.p. 90° (dec.);

j) 3-(alpha-phenyl-1-imidazolylmethyl)-benzonitrile; M/e 259; hydrochloride salt (hygroscopic), m.p. 80° (dec.);

The starting precursor for compound b is prepared as follows:

A solution of n-butyl lithium (20 ml of 2.4 M reagent, 0.048 mole) in hexane is added dropwise under an atmosphere of N_2 to a solution of N-tert-butyl-4-bromobenzamide (6.1 g, 0.024 mole) in THF (100 ml) which is maintained at -60° and then a solution of 4-chlorobenzaldehyde (5.1 g, 0.036 mole) in THF (50 ml) is added dropwise. The reaction mixture is stirred for 2 h at -60° and then quenched by the addition of saturated aqueous ammonium chloride (30 ml) and ether (100 ml). The ethereal layer is separated, washed repeatedly (3 x 30 ml) with aqueous sodium bisulfite and finally with brine and dried ($MgSO_4$). Solvent evaporation affords (4-chlorophenyl)-(4'-N-tert-butylcarbamoylphenyl)-methanol as an oil, NMR(CH methine) 4.30 ppm, which can be used without further purification.

The following carbinols are prepared in a similar manner using an appropriate starting material:

phenyl-(4'-N-tert-butylcarbamoylphenyl)-methanol, NMR(CH methine) 4.27 ppm;

(4-methoxyphenyl)-(4'-N-tert-butylcarbamoylphenyl)-methanol, NMR(CH methine) 4.23 ppm;

(2-methoxyphenyl)-(4'-N-tert-butylcarbamoylphenyl)-methanol, NMR(CH methine) 4.00 ppm;

(4-methylphenyl)-(4'-N-tert-butylcarbamoylphenyl)-methanol, NMR(CH methine) 4.23 ppm;

(3-pyridyl)-(4'-N-tert-butylcarbamoylphenyl)-methanol, NMR(CH methine) 4.20 ppm;

(2-thienyl)-(4'-N-tert-butylcarbamoylphenyl)-methanol, NMR(CH methine) 3.98 ppm;

(3-thienyl)-(4'-N-tert-butylcarbamoylphenyl)-methanol, NMR(CH methine) 4.05 ppm;

3-(alpha-hydroxybenzyl)-benzonitrile, NMR(CH methine) 4.20 ppm.

The appropriate starting cyanophenyl substituted chlorides corresponding to the above carbinols are prepared by treatment with thionyl chloride as previously described in Example 3.

Example 6:

A solution of 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile (5.3 g) in DMF (20 ml) is added dropwise to a cooled (ice-bath) stirred suspension of potassium tert-butoxide (2.5 g) in DMF (20 ml). This mixture is stirred for 30 min at 0-5° and then a solution of methyl iodide (3.5 g) in DMF (10 ml) is added

during 10 min. After stirring at 0-5° for a further 15 min, the reaction mixture is diluted with water (200 ml) and extracted with ethyl acetate (3 x 60 ml). The organic solution is washed with water (50 ml) and then extracted with 3N HCl (3 x 30 ml). The extracts are made basic (pH 8) with aqueous sodium hydroxide and the product is again extracted into ethyl acetate (2 x 50 ml). The extracts are dried ($MgSO_4$) and evaporated to give a solid which is recrystallized from isopropanol to give 4-[alpha-(4-cyanophenyl)-alpha-methyl-1-imidazolylmethyl]-benzonitrile, m.p. 184-186°.

Example 7:

a) A solution of boron tribromide (11.7 g) in dichloromethane (50 ml) is added dropwise during 30 min to a cooled (ice-bath) stirred solution of 4-[alpha-(4-methoxyphenyl-1-imidazolylmethyl]-benzonitrile (3.2 g) in dichloromethane (50 ml). The reaction is allowed to proceed at ambient temperature for 15 h and then the mixture is poured onto ice and water (100 ml). The pH is adjusted to 7 by the addition of solid sodium bicarbonate and the layers are separated. The organic solution is washed with water, dried ($MgSO_4$) and evaporated. The residual crude product is triturated with diethyl ether to give 4-[alpha-(4-hydroxyphenyl)-1-imidazolylmethyl]-benzonitrile, m.p. 196-198°.

b) 4-[alpha-(2-hydroxyphenyl)-1-imidazolylmethyl]-benzonitrile, m.p. 230-235° (dec.), is similarly prepared.

c) 4-[alpha-(4-hydroxybenzyl)-1-imidazolylmethyl]-benzonitrile, m.p. 238-240°, is also similarly prepared.

Example 8:

A solution containing 2-[alpha-(4-bromophenyl)-1-imidazolylmethyl]-benzonitrile (2.1 g) and hydrazine hydrate (10 ml) in 95% ethanol (60 ml) is mixed with 10% Pd-C catalyst (0.5 g) and the mixture is stirred at reflux for 2.5 h. The catalyst is filtered off and the solvent evaporated to give an oil which is dissolved in 3N HCl (20 ml). The acid solution is extracted with ethyl acetate (10 ml), neutralized to pH 7 with aqueous sodium hydroxide and extracted with ethyl acetate (3 x 10 ml). The extracts are dried ($MgSO_4$) and evaporated to give the crude product which is further purified by flash column chromatography on silica gel. Elution with ethyl acetate affords 2-[alpha-phenyl-1-imidazolylmethyl]-benzonitrile; IR(CN): 2240 cm^{-1}; M/e 259; hydrochloride salt, melting with dec.

Example 9:

A solution containing alpha-bromo-4-tolunitrile (19.6 g) and 1,2,4-triazole (30.5 g) in a mixture of chlorform (250 ml) and acetonitrile (50 ml) is stirred at reflux for 15 h. The solution is cooled and washed with 3% aqueous sodium bicarbonate (200 ml) and the organic solution is then dried ($MgSO_4$) and evaporated. The residue is chromatographed on silica gel (300 g). Elution with chloroform/isopropanol (10:1) affords 4-[1-(1,2,4-triazolyl)methyl]-benzonitrile, which forms a hydrochloride salt, m.p. 200-205°, when its solution in ethyl acetate is treated with ethereal HCl.

Further elution of the silica gel column with chloroform/isopropanol (3:2) affords 4-[1-(1,3,4-triazolyl)-methyl]-benzonitrile which forms a hydrochloride salt, m.p. 236-238°.

Example 10:

A solution containing alpha-bromo-4-tolunitrile (11.0 g), 1-(dimethylcarbamoyl)-4-methylimidazole (8.6 g) and sodium iodide (8.4 g) in acetonitrile (75 ml) is heated and stirred at reflux for 15 h. The mixture is cooled to 0° (ice-bath) and ammonia gas is bubbled through the solution for 15 min. The volatiles are then evaporated and the residue is partitioned between water (150 ml) and ethyl acetate (150 ml). The organic solution is washed with water (2 x 50 ml) and is then extracted with 3N HCl. The combined acidic extracts are made basic (pH 9) with 6N sodium hydroxide and the product is extracted into ethyl acetate (3 x 60 ml). After drying ($MgSO_4$), solvent evaporation affords crude 4-[1-(5-methylimidazolyl)methyl]-benzonitrile which forms a hydrochloride salt, m.p. 203-205°, when its solution in acetone is treated with ethereal HCl.

The starting material is prepared in the following manner:

A solution containing 4-methylimidazole (16.4 g), N,N-dimethylcarbamoyl chloride (30 g) and triethylamine (30 g) in acetonitrile (125 ml) is stirred at reflux for 20 h. Upon cooling, the reaction is diluted with diethyl ether (1000 ml) and then filtered. The filtrate is concentrated and the residue is distilled under reduced pressure. 1-(Dimethylcarbamoyl)-4-methylimidazole is obtained as a colorless liquid, b.p. 104-106° at 0.47 mbar.

Example 11:

a) A solution of n-butyl lithium (25 ml of 2.1 M reagent in hexane, 0.0525 mole) is added dropwise in an N_2 atmosphere to a solution of diisopropylamine (5.6 g) in THF (100 ml) which is maintained at -20°. This cold solution is then added dropwise to a solution of 4-(1-imidazolylmethyl)-benzonitrile (9.15 g) in THF (250 ml) which is maintained at -50° during addition and for 30 min subsequently. The reaction mixture is then cooled to -70° for 30 min and then without external cooling for 10 h. The reaction is quenched by addition of water (300 ml) and extracted with diethyl ether (3 x 100 ml). The combined ether extracts are extracted with 3N HCl (3 x 60 ml) and the acid extracts are made basic (pH 9) with 6N sodium hydroxide. The crude product is extracted into ether (3 x 60 ml), and after drying ($MgSO_4$) and solvent evaporation, 4-[1-(1-imidazolyl)ethyl]-benzonitrile is obtained. The crude material is dissolved in acetone and treated with ethereal HCl to afford the hydrochloride salt, m.p. 184-186°.

Similarly prepared are:

b) 4-[2-(1-imidazolyl)-2-propyl]-benzonitrile hydrochloride, m.p. 219-221°;
c) 4-(alpha-n-butyl-1-imidazolylmethyl)-benzonitrile oxalate, m.p. 73-75°;
d) 4-(alpha-isopropyl-1-imidazolylmethyl)-benzonitrile, m.p. 94-95°;
e) 4-(alpha-benzyl-1-imidazolylmethyl)-benzonitrile hydrochloride, m.p. 221-223°;
f) 4-[alpha-(4-cyanobenzyl)-1-imidazolylmethyl]-benzonitrile, m.p. 199-201°;

Example 12:

The lithium salt of 10.0 g of 4-(1-imidazolylmethyl)-benzonitrile is prepared in THF (250 ml) in the manner described in Example 11. This solution is cooled to -60° and solid paraformaldehyde (10.0 g, previously dried for 15 h in vacuo at 60°) is added, all at once. The reaction mixture is stirred at -60° for 1 h and then without cooling for a further 15 h. The reaction is then quenched with water (200 ml) and worked up in the manner described in Example 11 to afford a mixture of 4-(alpha-hydroxymethyl-1-imidazolylmethyl)-benzonitrile and 4-(alpha-methylene-1-imidazolylmethyl)-benzonitrile which is chromatographed on silica gel (250 g). Elution with a mixture of methylene chloride and isopropanol (19:1) affords 4-(alpha-methylene-1-imidazolylmethyl)-benzonitrile. This compound forms a hydrochloride salt, m.p. 195-197°, when its solution in acetone is treated with ethereal HCl.

Example 13:

a) Racemic 4-[1-(1-imidazolyl)ethyl]-benzonitrile (3.5 g) is dissolved in warm acetone (50 ml) and added to a solution of 1-tartaric acid (1.2 g) in warm acetone (300 ml). The mixture is allowed to stand at room temperature overnight and the tartrate salt is collected. This material is recrystallized four times from minimal volumes of anhydrous ethanol and the resultant material is converted to the free base by dissolution in water, making basic (pH 9) with dilute sodium hydroxide and isolating (-)-4-[1-(1-imidazolyl)ethyl]-benzonitrile which has an optical rotation $[\alpha]_D^{25} = -4.94°$.
b) (+)-4-[1-(1-Imidazolyl)ethyl]-benzonitrile is obtained in a similar manner using d-tartaric acid and has an optical rotation $[\alpha]_D^{25} = +4.89°$.

Each enantiomer forms a hydrochloride salt, m.p. 190-191°, when a solution in acetone is treated with ethereal HCl.

Example 14:

A solution of potassium tert-butoxide (1.10 g) in THF (50 ml) is added dropwise to a solution of 4-[1-(1-imidazolyl)-4-chlorobutyl]-benzonitrile (2.50 g) in THF at 0° (ice-bath). The reaction is allowed to proceed at 0° for 30 min and is then allowed to warm to room temperature during 3 h. The reaction is then quenched with water (100 ml) and the mixture is subsequently extracted with ethyl acetate (100 ml). The organic extract is extracted with 3N HCl (3 x 30 ml) and the combined acid extracts are made basic with 6N sodium hydroxide. The crude product is extracted into ethyl acetate (3 x 30 ml) and the combined extracts are dried ($MgSO_4$) and evaporated to afford 1-(4-cyanophenyl)-1-(1-imidazolyl)-cyclopentane as an oil. The compound is dissolved in acetone and treated with ethereal HCl to afford the hydrochloride salt, m.p. 217-219°.

The starting material, 4-[1-(1-imidazolyl)-4-chlorobutyl]-benzonitrile, is prepared as follows:
The lithium salt of 4-[1-imidazolylmethyl]-benzonitrile (3.7 g) is prepared at -50° in THF (100 ml) as described in Example 11, and the cold solution is then added dropwise to a solution of 1-chloro-4-

iodobutane (8.7 g) in THF (60 ml) at -60°. The reaction is maintained at -60° for 2 h and is then quenched by addition of water (150 ml). The product is extracted as described in Example 11 and the chlorobutyl intermediate is obtained as an oil. The methine-CH (triplet) is observed at 4.77 ppm in the NMR spectrum. The material is used without further purification.

Example 15:

A solution of potassium tert-butoxide (4.5 g) in THF (125 ml) is added dropwise during 1 h to a solution of 4-[1-imidazolylmethyl]-benzonitrile (3.66 g) and α,α'-dichloro-o-xylene (3.50 g) in THF (100 ml) which is maintained at 0° (ice-bath). The reaction mixture is subsequently stirred for a further 1 h without external cooling and is then quenched with water (200 ml) and extracted with ethyl acetate (150 ml). The organic extracts are then extracted with 3N HCl (3 x 80 ml) and the acidic extracts are made basic with 6N sodium hydroxide and the crude product is extracted into ethyl acetate (3 x 50 ml). The material obtained after drying ($MgSO_4$) and solvent evaporation is chromatographed on silica gel (100 g). Elution with ethyl acetate affords the crystalline 2-(4-cyanophenyl)-2-(1-imidazolyl)-indane which is recrystallized from isopropanol, m.p. 150-152°.

Example 16:

a) The lithium salt of 4-[1-imidazolylmethyl]-benzonitrile (3.7 g) is prepared at -50° in THF (100 ml) in the manner described in Example 11. This cold solution is then added dropwise to a solution of diphenyl disulfide (6.5 g) in THF (100 ml) at -50°. The reaction mixture is stirred for 2 h, then quenched by addition of water (150 ml) and worked up as described in Example 11 to afford 4-[alpha-phenylthio-1-imidazolylmethyl]-benzonitrile as an oil. The compound forms a hydrochloride salt, m.p. 159-162°, when its solution in ether is treated with ethereal HCl.

b) 4-[alpha-Methylthio-1-imidazolylmethyl]-benzonitrile hydrochloride, m.p. 137-140°, is similarly prepared.

Example 17:

2,2-Bis-(4-methoxyphenyl)-2-hydroxy-1-(1-imidazolyl)-1-(4-cyanophenyl)-ethane (10.2 g) is dissolved in thionyl chloride (25 ml) and the solution is stirred at room temperature for 36 h. The solvent is evaporated and the residue is chromatographed on silic gel (250 g). Elution with ethyl acetate affords the crystalline 2,2-bis-(4-methoxyphenyl)-1-(1-imidazolyl)-1-(4-cyanophenyl)-ethylene. The compound has m.p. 174-176° after recrystallization from isopropanol.

The starting material is prepared as follows:

The lithium salt of 4-(1-imidazolylmethyl)-benzonitrile (5.5 g) is prepared in THF (200 ml) in the manner described in Example 11. This cold solution is added dropwise to a solution of 4,4'-dimethoxybenzophenone (7.5 g) in THF (100 ml) at -60°. The reaction is allowed to proceed for 4 h at -60° and is then quenched by dropwise addition of acetic acid (0.5 ml) and then water (200 ml). After warming to room temperature, the mixture is diluted with ether (200 ml). The separated organic phase is washed with water (3 x 50 ml), dried over $MgSO_4$ and, after evaporating the solvents, the residue is chromatographed on silica gel (200 g). Elution with ethyl acetate affords 2,2-bis-(4-methoxyphenyl)-2-hydroxy-1-(1-imidazolyl)-1-(4-cyanophenyl)-ethane as a foam [NMR (CH-methine) 4.15 ppm].

Example 18:

Treatment of 2,2-bis-(4-methoxyphenyl)-1-(1-imidazolyl)-1-(4-cyanophenyl)-ethylene with boron tribromide using procedure analogous to that described in Example 7 yields 2,2-bis-(4-hydroxyphenyl)-1-(1-imidazolyl)-1-(4-cyanophenyl)-ethylene hydrobromide, m.p. 178° (dec.).

Example 19:

a) Zinc dust (23 g) is added in small portions over 15 min to a solution of 4-(alpha-chloro-3-pyridylmethyl)-benzonitrile hydrochloride (13.25 g) in a mixture of acetic acid (110 ml) and water (5 ml). The reaction mixture is stirred at room temperature for 3 h and is then filtered through a pad of Celite. The filtrate is concentrated and the residue is taken up in ether (250 ml) and washed with 3N sodium hydroxide (3 x 100 ml) and brine. After drying the ethereal solution (anhydrous Na_2SO_4), solvent

evaporation affords crude 4-(3-pyridylmethyl)-benzonitrile. The compound forms a hydrochloride salt, m.p. 155-157°, when its solution in ethyl acetate is treated with ethereal HCl.

The starting material is prepared from (3-pyridyl)-(4'-N-tert-butylcarbamoylphenyl)-methanol by treatment with thionyl chloride as described in Example 3.

Similarly prepared are:

b) 4-[alpha-(3-pyridyl)-3'-pyridylmethyl]-benzonitrile, m.p. 125-127°;

c) 4-[alpha-(4-pyridyl)-3'-pyridylmethyl]-benzonitrile oxalate, m.p. 172-174°.

Example 20:

a) 4-[1-(1,2,4-Triazolyl)methyl]-benzonitrile (Example 9/1) is reacted with potassium tert-butoxide and 4-fluorobenzonitrile according to procedure in Example 2 to yield 4-[alpha-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitrile, m.p. 181-183°.

b) 4-[1-(1,3,4-Triazolyl)methyl]-benzonitrile (Example 9/2) is similarly reacted with 4-fluorobenzonitrile to yield 4-[alpha-(4-cyanophenyl)-1-(1,3,4-triazolyl)methyl]-benzonitrile, m.p. 239-243°.

Example 21:

4-(3-Pyridylmethyl)-benzonitrile is reacted with potassium tert-butoxide and 4-fluorobenzonitrile according to the procedure in Example 2 to yield 4-[alpha-(4-cyanophenyl)-3-pyridylmethyl]-benzonitrile hydrochloride, m.p. 120-125° (dec.).

Example 22:

To 48.0 l of acetone under nitrogen is added 4.326 kg of potassium carbonate, 0.26 kg of potassium iodide, 3.2 kg of imidazole and 4.745 kg of alpha-chloro-4-tolunitrile. The mixture is stirred at 45° under nitrogen for 26 h. The reaction mixture is cooled, filtered and the solvent is evaporated at reduced pressure. The residue is redissolved in 40 l of methylene chloride, washed with 40 l of water and twice with 10 l of water. The organic phase is dried over magnesium sulfate and evaporated to yield the crude product which is stirred with 6.4 l of ether for 2 h. The solid is filtered, washed with 9 l of ether and dried at 40° and 26.7 mbar for 17 h to yield 4-(1-imidazolylmethyl)-benzonitrile, the compound of Example 1.

Example 23:

In portions of approximately 500 g, 4.44 kg of potassium tert-butoxide is added to 25 l of DMF, precooled to -10°, without allowing the solvent temperature to rise above -4°. The solution is recooled to -8° and a solution of 3.3 kg 4-(1-imidazolylmethyl)-benzonitrile in 12.5 l of DMF is added within 3.3 h. The rate of addition is adjusted to maintain the reaction temperature at -7 ± 2°.

The solution is stirred for 45 min while cooling to -11° and a solution of 2.18 kg of 4-fluorobenzonitrile in 5 l of DMF is added over 3.5 h. The reaction temperature is maintained at 3 ± 4°. After 1.25 h, the pH of the reaction is brought to 7 with 3.0 l of concentrated HCl, stirred an additional 20 min and allowed to stand overnight. The solvent is removed by distillation at 10.7 mbar over 7 h. The resulting oil is partitioned between 25 l of methylene chloride and 35 l of water. The layers are separated. The aqueous phase is extracted with 7 l of methylene chloride and the combined organic phases are washed with 10 l of H_2O and twice with 1.1 l of 3N HCl. The combined acidic layers are washed with 7 l of methylene chloride and added to a mixture of 10 kg of ice and 20 l of methyllene chloride. The solution is stirred and brought to pH 11 with 2.8 l of concentrated sodium hydroxide solution. The aqueous layer is separated and extracted with 5 l of methylene chloride. The combined organic phases are washed with 10 l of water and dried over magnesium sulfate. Filtration and evaporation at 45° and 10.7 mbar yields 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile as an oil; IR (CH_2Cl_2) 2240 cm^{-1}.

A solution of 9.23 kg of the above free base in 19.1 l of isopropanol is treated with 0.45 kg of decolorizing carbon and after 15 min is filtered into a stirred solution of 1.84 kg of succinic acid in 31.4 l of isopropanol at 50°. The solution is stirred for 14 h at 50° and allowed to cool to room temperature. The resulting crystalline solid is collected by filtration, washed with 8 l of isopropanol and 5 l of diethyl ether and dried at 90° and 26.7 mbar for 28 h to yield 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile hemisuccinate, m.p. 149-150°. Recrystallization from isopropanol/ether gives product melting at 151-152°.

Example 24:

Preparation of 10,000 tablets each containing 5 mg of the active ingredient:

Formula:

4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile hemisuccinate	50.00 g
Lactose	2535.00 g
Corn starch	125.00 g
Polyethylene glycol 6,000	150.00 g
Magnesium stearate	40.00 g
Purified water	q.s.

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance, lactose, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the suspension is added to the boiling solution of the polyethylene glycol in 260 ml of water. The paste formed is added to the powders, which are granulated, if necessary, with an additional amount of water. The granulate is dried overnight at 35°, broken on a screen with 1.2 mm openings and compressed into tablets, using concave uppers bisected.

Analogously tablets are prepared containing one of the other compounds disclosed and exemplified herein.

Example 25:

Preparation of 1,000 capsules each containing 10 mg of the active ingredient:

Formula:

4-[alpha-(3-pyridyl)-1-imidazolylmethyl]-benzonitrile dihydrochloride	10.0 g
Lactose	207.0 g
Modified starch	80.0 g
Magnesium stearate	3.0 g

Procedure:

All the powders are passed through a screen with openings of 0.6 mm. Then the drug substance is placed in a suitable mixer and mixed first with the magnesium stearate, then with the lactose and starch until homogeneous. No. 2 hard gelatin capsules are filled with 300 mg of said mixture each, using a capsule filling machine.

Analogously capsules are prepared, containing one of the other compounds disclosed and exemplified herein.

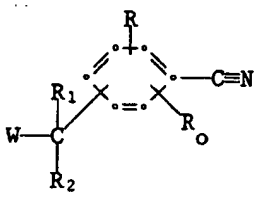
Example 26:

10 ml of 2N sulfuric acid are added to a solution of 2.60 g (10 mmole) 4-[alpha-(3-pyridyl)-1-imidazolylmethyl]-benzonitrile, the compound of example 5e), in 100 ml of ethanol, while stirring and cooling the solution in an ice bath; immediately crystals precipitate. After filtration, washing with ethanol and drying under high vacuum, 4-[alpha-(3-pyridyl)-1-imidazolylmethyl]-benzonitrile sulfate, m.p. 238-240°, is obtained.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Use of a compound of the formula I



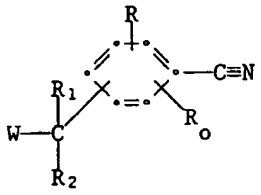
(I)

wherein R and R_0 independently represent hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 and R_2 independently represent hydrogen, lower alkyl, (lower alkyl, aryl or aryl-lower alkyl)-thio, lower alkenyl, aryl, aryl-lower alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkyl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene, mono- or di-aryl-lower alkylidene; R_1 and R_2 combined also represent C_4-C_6-straight chain alkylene, lower alkyl-substituted straight chain alkylene or ortho-phenylene bridged-C_2-C_4-straight chain alkylene, each forming with the carbon atom attached thereto a corresponding optionally substituted or benzo-fused 5-, 6- or 7-membered ring; W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl; or W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl substituted by lower alkyl;
and aryl within the above definitions represents phenyl which is unsubstituted or substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, aroyloxy, lower alkoxycarbonyloxy, N,N-di-lower alkylcarbamoyloxy, nitro, amino, halo, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, (phenyl, naphthyl, pyridyl, thienyl, indolyl or furyl)-lower alkoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, 3-phthalidoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, aroyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; 1- or 2-naphthyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, cyano or halo; a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl; or a said heterocyclic aromatic radical which is monosubstituted by lower alkyl, lower alkoxy, cyano or halo;
and aroyl within the above definitions represents benzoyl which is unsubstituted or substituted by one or two of lower alkyl, lower alkoxy, halo or trifluormethyl; thienoyl, pyrroloyl or 2-, 3- or 4-pyridylcarbonyl;
and radicals designated as "lower" contain up to and including 7 carbon atoms;
or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical preparation for the treatment of diseases responsive to aromatase inhibition.

2. Use according to claim 1 of a compound of formula I, wherein R and R_0 represent independently hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl or lower alkenyl; R_2 represents hydrogen, lower alkyl, aryl, aryl-lower alkyl, (lower alkyl, aryl or aryl-lower alkyl)-thio or lower alkenyl; or R_1 and R_2 combined represent lower alkylidene or C_4-C_6-alkylene; and W has meaning as given in claim 1; and aryl within the above definitions represents phenyl or phenyl substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halo, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, sulfamoyl, N-lower-alkylsulfamoyl or N,N-di-lower alkylsulfamoyl; or a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl, or a said heterocyclic radical monosubstituted by lower alkyl, lower alkoxy, cyano or halo; or a pharmaceutically acceptable salt thereof.

3. Use according to claim 2 of a compound of formula I, wherein R_1 represents hydrogen; and W, R, R_0, R_2 as well as R_1 and R_2 combined have meaning as given in claim 2.

4. Compounds of the formula I



(I)

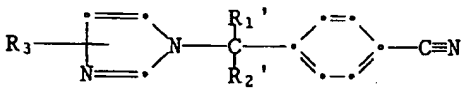
wherein R and R_0 independently represent hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 represents hydrogen; R_2 represents hydrogen, lower alkyl, lower alkenyl, aryl, aryl-lower alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkyl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene, or mono- or di-aryl-lower alkylidene; R_1 and R_2 combined also represent C_4-C_6-straight chain alkylene, lower alkyl-substituted straight chain alkylene or ortho-phenylene bridged-C_2-C_4-straight chain alkylene, to form with the carbon atom attached thereto a corresponding optionally substituted or benzo-fused 5-, 6- or 7-membered ring; W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl; or W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl substituted by lower alkyl;
and aryl within the above definitions represents phenyl which is unsubstituted or substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, aroyloxy, lower alkoxycarbonyloxy, N,N-di-lower alkylcarbamoyloxy, nitro, amino, halo, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, (phenyl, naphthyl, pyridyl, thienyl, indolyl or furyl)-lower alkoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, 3-phthalidoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, aroyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; 1- or 2-naphthyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, cyano or halo; a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl; or a said heterocyclic aromatic radical which is monosubstituted by lower alkyl, lower alkoxy, cyano or halo;
and aroyl within the above definitions represents benzoyl which is unsubstituted or substituted by one or two of lower alkyl, lower alkoxy, halo or trifluormethyl; thienoyl, pyrroloyl or 2-, 3- or 4-pyridylcarbonyl;
and radicals designated as "lower" contain up to and including 7 carbon atoms;
and pharmaceutically acceptable salts thereof.

5. Compounds according to claim 4 of the formula I, wherein R and R_0 represent hydrogen; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene ring; R_1 represents hydrogen; R_2 represents hydrogen, lower alkyl, aryl or aryl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene or di-aryl-lower alkylidene; R_1 and R_2 combined also represent C_4-C_6-straight chain alkylene or ortho-phenylene bridged-C_2-C_4-straight chain alkylene, to form with the carbon atom attached thereto a corresponding optionally benzo-fused 5-, 6- or 7-membered ring; W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl, 3-pyridyl, or 1-imidazolyl substituted by lower alkyl; and aryl within the above definitions represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, hydroxy, halo, trifluoromethyl or cyano; thienyl or pyridyl; and pharmaceutically acceptable salts thereof.

6. Compounds according to claim 4 of the formula I, wherein R and R_0 independently represent hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 represents hydrogen; R_2 represents hydrogen, lower alkyl, lower alkenyl, aryl, or aryl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene or C_4-C_6-alkylene; W represents 1-imidazolyl or 1-imidazolyl substituted by lower alkyl; and aryl within the above definitions represents phenyl or phenyl substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halo, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl or N,N-di-lower alkylsulfamoyl; or aryl within the above definitions also represents a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl, or a said

heterocyclic radical monosubstituted by lower alkyl, lower alkoxy, cyano or halo; and pharmaceutically acceptable salts thereof.

7. Compounds according to claim 4 of the formula II



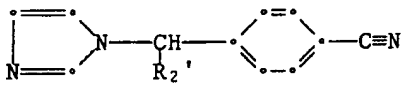
(II)

wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, pyridyl, thienyl or benzyl; or R_2' represents phenyl or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halo, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono-or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene or diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

8. Compounds according to claim 7 of the formula II, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, pyridyl, benzyl or phenyl; or R_2' represents benzyl or phenyl, each monosubstituted on phenyl by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halo, nitro, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

9. Compounds according to claim 7 of the formula II, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl, each monosubstituted on phenyl by cyano, halo, lower alkoxy, lower alkyl or trifluoromethyl; R_3 represents hydrogen or lower alkyl at the 4- or 5-position; and pharmaceutically acceptable salts thereof.

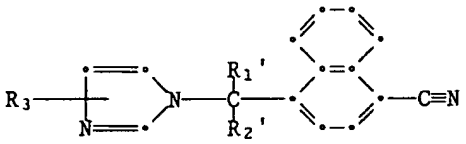
10. Compounds according to claim 4 of the formula III



(III)

wherein R_2' represents 3-pyridyl, p-cyanobenzyl or p-cyanophenyl; and pharmaceutically acceptable salts thereof.

11. Compounds of the formula IV



(IV)

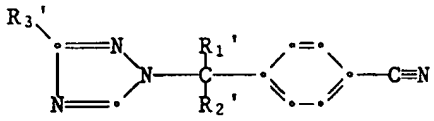
wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, lower alkylthio, phenyl-lower alkylthio, phenylthio, pyridyl, thienyl or benzyl; or R_2' represents phenyl, phenyl-lower alkylthio, phenylthio or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halo, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene, diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

12. Compounds according to claims 4 and 11 of the formula IV, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, pyridyl; or R_2' represents benzyl or phenyl, each unsubstituted or monosubstituted on phenyl by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halo, nitro, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

13. Compounds according to claim 12 of the formula IV, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl, each monosubstituted on phenyl by cyano, halo, lower alkoxy, lower alkyl or trifluoromethyl; R_3 represents hydrogen or lower alkyl at the 4- or 5-position; and pharmaceutically acceptable salts thereof.

14. Compounds according to claim 12 of the formula IV, wherein R_1' and R_3 represent hydrogen; R_2' represents 3-pyridyl, p-cyanobenzyl or p-cyanophenyl; and pharmaceutically acceptable salts thereof.

15. Compounds according to claim 4 of the formula V



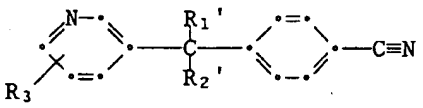
(V)

wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, pyridyl, thienyl or benzyl; or R_2' represents phenyl or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halo, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono-or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene or diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3' represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

16. Compounds according to claim 15 of the formula V, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl, each monosubstituted on phenyl by cyano, halo, lower alkoxy, lower alkyl or trifluoromethyl; R_3' represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

17. Compounds according to claim 15 of the formula V, wherein R_1' and R_3' represent hydrogen; R_2' represents 3-pyridyl, p-cyanobenzyl or p-cyanophenyl; and pharmaceutically acceptable salts thereof.

18. Compounds of the formula VI



(VI)

wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, lower alkylthio, phenyl-lower alkylthio, phenylthio, pyridyl, thienyl, benzyl; or R_2' represents phenyl, phenyl-lower alkylthio, phenylthio or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halo, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene or diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

19. Compounds according to claims 4 and 18 of the formula VI, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, pyridyl; or R_2' represents benzyl or phenyl each unsubstituted or monosubstituted on phenyl by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halo, nitro,

trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; R_3 represents hydrogen or lower alkyl; and pharmaceutically acceptable salts thereof.

20. Compounds according to claim 19 of the formula VI, wherein R_1' and R_3 represent hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl each substituted on phenyl by cyano, halo, lower alkoxy, lower alkyl or trifluoromethyl; and pharmaceutically acceptable salts thereof.

21. Compounds according to claim 19 of the formula VI, wherein R_1' and R_3 represent hydrogen; R_2' represents 3- or 4-pyridyl, p-cyanobenzyl or p-cyanophenyl; and pharmaceutically acceptable salts thereof.

22. A compound of claim 4 being 4-(alpha-isopropyl-1-imidazolylmethyl)-benzonitrile, a stereoisomer or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

23. A compound of claim 4 being 4-[alpha-(3-pyridyl)-1-imidazolylmethyl]-benzonitrile, a stereoisomer or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

24. A compound of claim 4 being 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile, or a pharmaceutically acceptable salt thereof.

25. A compound of claim 4 being 4-(alpha-benzyl-1-imidazolylmethyl)-benzonitrile, a stereoisomer or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof.

26. A compound of claim 4 being 2-(4-cyanophenyl)-2-(1-imidazolyl)-indane, or a pharmaceutically acceptable salt thereof.

27. A compound of claim 4 being 4-[alpha-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitrile, or a pharmaceutically acceptable salt thereof.

28. Pharmaceutical preparations comprising a compound according to any one of claims 4-27 together with a pharmaceutically acceptable carrier.

29. A compound according to any one of claims 4-27 for use in a method for the therapeutic treatment of the animal or human body.

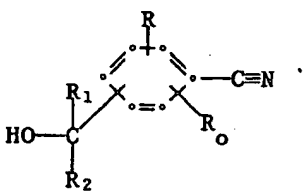
30. The use of a compound according to any one of claims 4-27 for the manufacture of a pharmaceutical preparation for the treatment of conditions responsive to inhibitors of aromatase activity.

31. Process for the manufacture of the compounds of the formula I according to claim 4, or salts thereof, which comprises

a) for compounds of formula I wherein W represents 1-imidazolyl or 1-triazolyl each optionally substituted by lower alkyl, condensing a compound of the formula VII

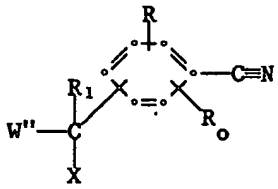
W'-H (VII)

wherein W' represents 1-imidazolyl or 1-triazolyl each optionally substituted by lower alkyl, or an N-protected derivative thereof, with a reactive esterified derivative of a compound of the formula VIII,



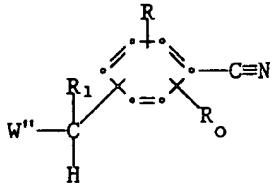
(VIII)

wherein R, R_0, R_1 and R_2 have meaning as defined herein for formula I;
b) for compounds wherein W represents 3-pyridyl optionally substituted by lower alkyl, dehalogenating a compound of the formula IX



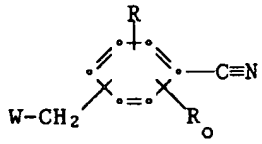
(IX)

wherein W" represents 3-pyridyl optionally substituted by lower alkyl, X represents halogen, preferably chloro, R and R_0 have leaning as defined herein for compounds of formula I and R_1 has meaning as defined herein for formula I; and if required reacting the resulting product of formula X



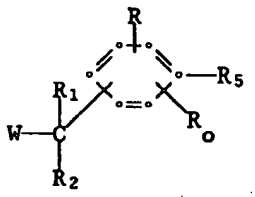
(X)

with a reactive derivative of the radical R_2 using process c) below;
c) condensing under basic conditions a compound of the formula XI,



(XI)

(being a compound of formula I wherein R_1 and R_2 represent hydrogen)
wherein R, R_0 and in have meaning as defined herein for formula I, with a reactive functional derivative of a radical R_1 or R_2 (R_1 or R_2 not representing hydrogen), so as to obtain a compound of formula I wherein only one of R_1 and R_2 represents hydrogen; or similarly condensing a compound of formula I so obtained with a reactive functional derivative of a radical R_1 or R_2 (R_1 or R_2 not representing hydrogen) to obtain a compound of formula I wherein neither R_1 nor R_2 represents hydrogen; or condensing a compound of the formula XI with a reactive bifunctional derivative of R_1 and R_2 combined representing C_4-C_6 straight alkylene, lower alkyl substituted C_4-C_6 straight chain alkylene or 1,2-phenylene-bridged-C_2-C_4 straight chain alkylene to obtain a corresponding compound of formula I;
d) converting R_5 to cyano in a compound of the formula XII,

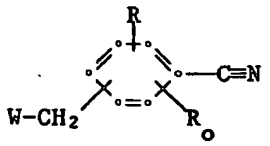


(XII)

wherein W, R, R_0, R_1 and R_2 have meaning as defined above and R_5 represents a group or radical that can be converted to the cyano group;
and/or converting a compound of formula I into another compound of formula I; and/or converting a free compound into a salt, and/or converting a salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates into the single isomers or racemates and/or resolving

a racemate into the optical isomers.

32. A process according to claim 31 for the manufacture of a compound of the formula I wherein R_1 represents hydrogen; R_2 represents 4-cyanophenyl; W, R and R_0 have meaning as defined in said claim; which comprises condensing under basic conditions a compound of the formula XI



(XI)

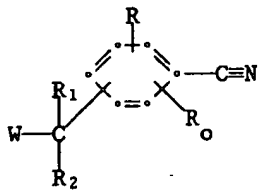
with p-fluorobenzonitrile.

33. A process according to claim 32 for the manufacture of 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile.

34. A process according to claim 32 for the manufacture of 4-[alpha-(4-cyanophenyl)-1-(1,2,4-triazolyl)-methyl]-benzonitrile.

Claims for the following Contracting States : AT, ES, GR

1. Process for the manufacture of a compound of the formula I



(I)

wherein R and R_0 independently represent hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 represents hydrogen; R_2 represents hydrogen, lower alkyl, lower alkenyl, aryl, aryl-lower alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkyl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene, or mono- or di-aryl-lower alkylidene; R_1 and R_2 combined also represent C_4-C_6-straight chain alkylene, lower alkyl-substituted straight chain alkylene or ortho-phenylene bridged-C_2-C_4-straight chain alkylene, to form with the carbon atom attached thereto a corresponding optionally substituted or benzo-fused 5-, 6- or 7-membered ring; W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl; or W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl or 3-pyridyl substituted by lower alkyl;

and aryl within the above definitions represents phenyl which is unsubstituted or substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, aroyloxy, lower alkoxycarbonyloxy, N,N-di-lower alkylcarbamoyloxy, nitro, amino, halo, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, (phenyl, naphthyl, pyridyl, thienyl, indolyl or furyl)-lower alkoxycarbonyl, lower alkanoyloxy-lower alkoxycarbonyl, 3-phthalidoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, aroyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl and N,N-di-lower alkylsulfamoyl; 1- or 2-naphthyl which is unsubstituted or substituted by lower alkyl, lower alkoxy, cyano or halo; a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl; or a said heterocyclic aromatic radical which is monosubstituted by lower alkyl, lower alkoxy, cyano or halo;

and aroyl within the above definitions represents benzoyl which is unsubstituted or substituted by one or two of lower alkyl, lower alkoxy, halo or trifluormethyl; thienoyl, pyrroloyl or 2-, 3- or 4-pyridylcarbonyl;

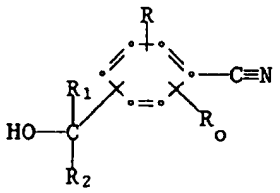
and radicals designated as "lower" contain up to and including 7 carbon atoms;

or a pharmaceutically acceptable salt thereof, which comprises

a) for compounds of formula I wherein W represents 1-imidazolyl or 1-triazolyl each optionally substituted by lower alkyl, condensing a compound of the formula VII

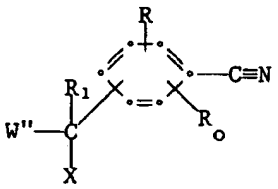
W'-H (VII)

wherein W' represents 1-imidazolyl or 1-triazolyl each optionally substituted by lower alkyl, or an N-protected derivative thereof, with a reactive esterified derivative of a compound of the formula VIII,



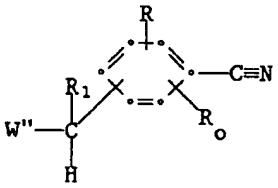
(VIII)

wherein R, R_0, R_1 and R_2 have meaning as defined herein for formula I;
b) for compounds wherein W represents 3-pyridyl optionally substituted by lower alkyl, dehalogenating a compound of the formula IX



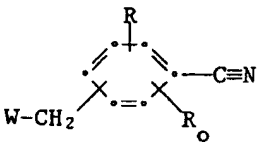
(IX)

wherein W" represents 3-pyridyl optionally substituted by lower alkyl, X represents halogen, preferably chloro, R and R_0 have meaning as defined herein for compounds of formula I and R_1 has meaning as defined herein for formula I; and if required reacting the resulting product of formula X



(X)

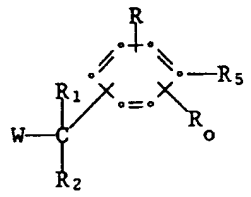
with a reactive derivative of the radical R_2 using process c) below;
c) condensing under basic conditions a compound of the formula XI,



(XI)

(being a compound of formula I wherein R_1 and R_2 represent hydrogen)
wherein R, R_0 and W have meaning as defined herein for formula I, with a reactive functional derivative of a radical R_1 or R_2 (R_1 or R_2 not representing hydrogen), so as to obtain a compound of formula I wherein only one of R_1 and R_2 represents hydrogen; or similarly condensing a compound of formula I so obtained with a reactive functional derivative of a radical R_1 or R_2 (R_1 or R_2 not representing hydrogen) to obtain a compound of formula I wherein neither R_1 nor R_2 represents hydrogen; or condensing a compound of the formula XI with a reactive bifunctional derivative of R_1 and R_2 combined representing C_4-C_6 straight alkylene, lower alkyl substituted C_4-C_6 straight chain

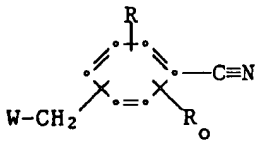
alkylene or 1,2-phenylene-bridged-C_2-C_4 straight chain alkylene to obtain a corresponding compound of formula I;
d) converting R_5 to cyano in a compound of the formula XII,



(XII)

wherein W, R, R_0, R_1 and R_2 have meaning as defined above and R_5 represents a group or radical that can be converted to the cyano group;
and/or converting a compound of formula I into another compound of formula I; and/or converting a free compound into a salt, and/or converting a salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates into the single isomers or racemates and/or resolving a racemate into the optical isomers.

2. A process according to claim 1 for the manufacture of a compound of the formula I wherein R_1 represents hydrogen; R_2 represents 4-cyanophenyl; W, R and R_0 have meaning as defined in said claim; which comprises condensing under basic conditions a compound of the formula XI



(XI)

with p-fluorobenzonitrile.

3. A process according to claim 2 for the manufacture of 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile.

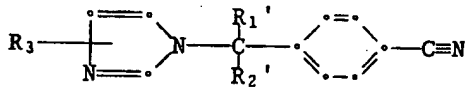
4. A process according to claim 2 for the manufacture of 4-[alpha-(4-cyanophenyl)-1-(1,2,4-triazolyl)-methyl]-benzonitrile.

5. Process according to claim 1 for the manufacture of a compound of the formula I, wherein R and R_0 represent hydrogen; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene ring; R_1 represents hydrogen; R_2 represents hydrogen, lower alkyl, aryl or aryl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene or di-aryl-lower alkylidene; R_1 and R_2 combined also represent C_4-C_6-straight chain alkylene or ortho-phenylene bridged-C_2-C_4-straight chain alkylene, to form with the carbon atom attached thereto a corresponding optionally benzo-fused 5-, 6- or 7-membered ring; W represents 1-imidazolyl, 1-(1,2,4 or 1,3,4)-triazolyl, 3-pyridyl, or 1-imidazolyl substituted by lower alkyl; and aryl within the above definitions represents phenyl or phenyl substituted by lower alkyl, lower alkoxy, hydroxy, halo, trifluoromethyl or cyano; thienyl or pyridyl; or a pharmaceutically acceptable salt thereof.

6. Process according to claim 1 for the manufacture of a compound of the formula I, wherein R and R_0 independently represent hydrogen or lower alkyl; or R and R_0 located on adjacent carbon atoms and together when combined with the benzene ring to which they are attached form a naphthalene or tetrahydro-naphthalene ring; R_1 represents hydrogen; R_2 represents hydrogen, lower alkyl, lower alkenyl, aryl, or aryl-lower alkyl; or R_1 and R_2 combined represent lower alkylidene or C_4-C_5-alkylene; W represents 1-imidazolyl or 1-imidazolyl substituted by lower alkyl; and aryl within the above definitions represents phenyl or phenyl substituted by one or two substituents selected from lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, nitro, amino, halo, trifluoromethyl, cyano, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, sulfamoyl, N-lower alkylsulfamoyl or N,N-di-lower alkylsulfamoyl; or aryl within

the above definitions also represents a heterocyclic aromatic radical selected from thienyl, indolyl, pyridyl and furyl, or a said heterocyclic radical monosubstituted by lower alkyl, lower alkoxy, cyano or halo; or a pharmaceutically acceptable salt thereof.

7. Process according to claim 1 for the manufacture of a compound of the formula II



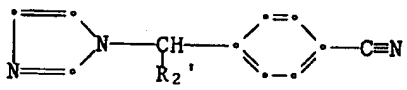
(II)

wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, pyridyl, thienyl or benzyl; or R_2' represents phenyl or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halo, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono-or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene or diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3 represents hydrogen or lower alkyl; or a pharmaceutically acceptable salt thereof.

8. Process according to claim 7 for the manufacture of a compound of the formula II, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, pyridyl, benzyl or phenyl; or R_2' represents benzyl or phenyl, each monosubstituted on phenyl by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halo, nitro, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; R_3 represents hydrogen or lower alkyl; or a pharmaceutically acceptable salt thereof.

9. Process according to claim 7 for the manufacture of a compound of the formula II, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl, each monosubstituted on phenyl by cyano, halo, lower alkoxy, lower alkyl or trifluoromethyl; R_3 represents hydrogen or lower alkyl at the 4- or 5-position; or a pharmaceutically acceptable salt thereof.

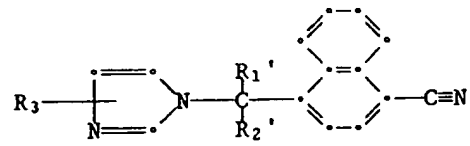
10. Process according to claim 1 for the manufacture of a compound of the formula III



(III)

wherein R_2' represents 3-pyridyl, p-cyanobenzyl or p-cyanophenyl; or a pharmaceutically acceptable salt thereof.

11. Process for the manufacture of a compound of the formula IV



(IV)

wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, lower alkylthio, phenyl-lower alkylthio, phenylthio, pyridyl, thienyl or benzyl; or R_2' represents phenyl, phenyl-lower alkylthio, phenylthio or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halo, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene, diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3 represents hydrogen or lower alkyl; or a pharmaceutically acceptable salt thereof, said process being carried out in

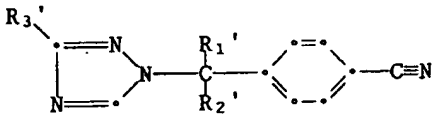
accordance with any one of processes a), c) or d) mentioned in claim 1, using starting materials that carry the appropriate substituents for obtaining the compounds of formula IV, and/or converting a compound of formula IV into another compound of formula IV; and/or converting a free compound into a salt, and/or converting a salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates into the single isomers or racemates and/or resolving a racemate into the optical isomers.

12. Process according to claim 11 for the manufacture of a compound of the formula IV, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, pyridyl; or R_2' represents benzyl or phenyl, each unsubstituted or monosubstituted on phenyl by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halo, nitro, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di)-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; R_3 represents hydrogen or lower alkyl; or a pharmaceutically acceptable salt thereof.

13. Process according to claim 12 for the manufacture of a compound of the formula IV, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl, each monosubstituted on phenyl by cyano, halo, lower alkoxy, lower alkyl or trifluoromethyl; R_3 represents hydrogen or lower alkyl at the 4- or 5-position; or a pharmaceutically acceptable salt thereof.

14. Process according to claim 12 for the manufacture of a compound of the formula IV, wherein R_1' and R_3 represent hydrogen; R_2' represents 3-pyridyl, p-cyanobenzyl or p-cyanophenyl; or a pharmaceutically acceptable salt thereof.

15. Process according to claim 1 for the manufacture of a compound of the formula V



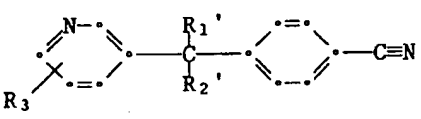
(V)

wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, pyridyl, thienyl or benzyl; or R_2' represents phenyl or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halo, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono-or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene or diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3' represents hydrogen or lower alkyl; or a pharmaceutically acceptable salt thereof.

16. Process according to claim 15 for the manufacture of a compound of the formula V, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl, each monosubstituted on phenyl by cyano, halo, lower alkoxy, lower alkyl or trifluoromethyl; R_3' represents hydrogen or lower alkyl; or a pharmaceutically acceptable salt thereof.

17. Process according to claim 15 for the manufacture of a compound of the formula V, wherein R_1' and R_3' represent hydrogen; R_2' represents 3-pyridyl, p-cyanobenzyl or p-cyanophenyl; or a pharmaceutically acceptable salt thereof.

18. Process for the manufacture of a compound of the formula VI



(VI)

wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, phenyl, lower alkylthio, phenyl-lower alkylthio, phenylthio, pyridyl, thienyl, benzyl; or R_2' represents phenyl, phenyl-lower alkylthio,

phenylthio or benzyl, each monosubstituted on the phenyl ring by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, benzoyloxy, nitro, halo, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; or R_1' and R_2' combined represent together lower alkylidene, benzylidene or diphenylmethylidene; or R_1' and R_2' combined represent together C_4-C_6 straight chain alkylene; R_3 represents hydrogen or lower alkyl; or a pharmaceutically acceptable salt thereof, said process being carried out in accordance with any one of processes a), b), c) or d) mentioned in claim 1, using starting materials that carry the appropriate substituents for obtaining the compounds of formula VI, and/or converting a compound of formula VI into another compound of formula VI; and/or converting a free compound into a salt, and/or converting a salt into a free compound or into another salt; and/or separating a mixture of isomers or racemates into the single isomers or racemates and/or resolving a racemate into the optical isomers.

19. Process according to claim 18 for the manufacture of a compound of the formula VI, wherein R_1' represents hydrogen; R_2' represents hydrogen, lower alkyl, pyridyl; or R_2' represents benzyl or phenyl each unsubstituted or monosubstituted on phenyl by cyano, lower alkyl, lower alkoxy, hydroxy, lower alkanoyloxy, halo, nitro, trifluoromethyl, lower alkanoyl, benzoyl, lower alkylsulfonyl, carbamoyl, N-mono- or N,N-di-lower alkylcarbamoyl, sulfamoyl, N-mono- or N,N-di-lower alkylsulfamoyl; R_3 represents hydrogen or lower alkyl; or a pharmaceutically acceptable salt thereof.

20. Process according to claim 19 for the manufacture of a compound of the formula VI, wherein R_1' and R_3 represent hydrogen; R_2' represents hydrogen, lower alkyl, benzyl, phenyl, or 3- or 4-pyridyl; or R_2' represents phenyl or benzyl each substituted on phenyl by cyano, halo, lower alkoxy, lower alkyl or trifluoromethyl; or a pharmaceutically acceptable salt thereof.

21. Process according to claim 19 for the manufacture of a compound of the formula VI, wherein R_1' and R_3 represent hydrogen; R_2' represents 3- or 4-pyridyl, p-cyanobenzyl or p-cyanophenyl; or a pharmaceutically acceptable salt thereof.

22. Process according to claim 1, characterized in that 4-(alpha-isopropyl-1-imidazolylmethyl)-benzonitrile, a stereoisomer or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, is manufactured.

23. Process according to claim 1, characterized in that 4-[alpha-(3-pyridyl)-1-imidazolylmethyl]-benzonitrile, a stereoisomer or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, is manufactured.

24. Process according to claim 1, characterized in that 4-[alpha-(4-cyanophenyl)-1-imidazolylmethyl]-benzonitrile, or a pharmaceutically acceptable salt thereof, is manufactured.

25. Process according to claim 1, characterized in that 4-(alpha-benzyl-1-imidazolylmethyl)-benzonitrile, a stereoisomer or a mixture of stereoisomers thereof, or a pharmaceutically acceptable salt thereof, is manufactured.

26. Process according to claim 1, characterized in that 2-(4-cyanophenyl)-2-(1-imidazolyl)-indane, or a pharmaceutically acceptable salt thereof, is manufactured.

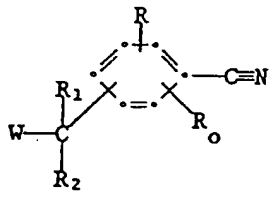
27. Process according to claim 1, characterized in that 4-[alpha-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitrile, or a pharmaceutically acceptable salt thereof, is manufactured.

28. Process for the manufacture of a pharmaceutical preparation, which comprises incorporating a compound obtainable according to any one of claims 1-27 into said preparations with a percentage of 1-50 %.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verwendung einer Verbindung der Formel (I),



(I)

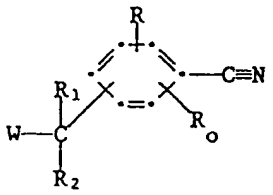
worin R und R_0 unabhängig voneinander Wasserstoff oder Niederalkylgruppen bedeuten, oder R und R_0, wenn sie an benachbarten Kohlenstoffatomen angeordnet sind, zusammen und mit dem Benzolring, an den sie gebunden sind, einen Naphthalin- oder Tetrahydronaphthalinring bilden; R_1 und R_2 unabhängig voneinander Wasserstoff, Niederalkylgruppen, (Niederalkyl-, Aryl- oder Aryl-Niederalkyl-)-thiogruppen, Niederalkenylgruppen, Aryl-, Aryl-Niederalkylgruppen, C_3-C_6-Cycloalkyl- oder C_3-C_6-Cycloalkyl-Niederalkylgruppen bedeuten, oder R_1 und R_2 zusammen Niederalkyliden-, Mono-oder Diaryl-Niederalkylidengruppen darstellen; oder R_1 und R_2 zusammen auch C_4-C_6-geradkettige Alkylengruppen, durch Niederalkylgruppen substituierte geradkettige Alkylengruppen oder o-Phenylengruppen mit einer C_2-C_4-geradkettigen Alkylenbrücke darstellen, von denen jede mit dem Kohlenstoffatom, an das sie gebunden sind, einen entsprechenden, gegebenenfalls substituierten oder Benzo-kondensierten 5-, 6- oder 7-gliedrigen Ring bilden; W eine 1-Imidazolyl-, 1-(1,2,4- oder 1,3,4-)-Triazolyl- oder 3-Pyridylgruppe bedeutet, oder W durch Niederalkylgruppen substituierte 1-Imidazolyl-, 1-(1,2,4- oder 1,3,4-)-Triazolyl- oder 3-Pyridylgruppen bedeutet; und wobei in den vorstehend genannten Definitionen Aryl Phenyl bedeutet, das gegebenenfalls mit ein oder zwei Substituenten, ausgewählt aus Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Aroyloxy-, Niederalkoxycarbonyloxy-, N,N-Di-Niederalkylcarbamoyloxy-, Nitro-, Amino-, Halogen-, Trizluormethyl-, Cyano-, Carboxy-, Niederalkoxycarbonyl, (Phenyl-, Naphthyl-, Pyridyl-, Thienyl-, Indolyl- oder Furyl-)-Niederalkoxycarbonyl-, Niederalkanoyl-Niederalkoxycarbonyl-, 3-Phthalidoxycarbonyl-, Carbamoyl-, N-Niederalkylcarbamoyl-, N,N-Di-Niederalkylcarbamoyl-, Niederalkanoyl-, Aroyl-, Niederalkylsulfonyl-, Sulfamoyl-, N-Niederalkylsulfamoyl- und N,N-Di-Niederalkylsulfamoylgruppen; 1- oder 2-Naphthylgruppen, gegebenenfalls substituiert mit Niederalkyl-, Niederalkoxy-, Cyano- oder Halogengruppen; einen heterocyclischen aromatischen Rest, ausgewählt aus Thienyl-, Indolyl-, Pyridyl- und Furylgruppen; oder der heterocyclische aromatische Rest monosubstituiert ist mit Niederalkyl-, Niederalkoxy-, Cyano- oder Halogengruppen, bedeutet; und Aroyl in den vorstehenden Definitionen eine Benzoylgruppe, gegebenenfalls substituiert mit ein oder zwei Niederalkyl-, Niederalkoxy-, Halogen- oder Trifluormethylgruppen; Thienoyl-, Pyrroloyl- oder 2-, 3- oder 4-Pyridylcarbonylgruppen, bedeutet; und Reste, die mit "Nieder" bezeichnet werden bis zu und einschließlich 7 Kohlenstoffatome enthalten, sowie pharmazeutisch verträgliche Salze davon; zur Herstellung eines Arzneimittels zur Behandlung von Erkrankungen, die auf Aromatasehemmung ansprechen.

2. Verwendung nach Anspruch 1 einer Verbindung der Formel (I), in der R und R_0 unabhängig voneinander Wasserstoff oder Niederalkylgruppen bedeuten; oder in der R und R_0, die an benachbarten Kohlenstoffatomen stehen und zusammen mit dem Benzolring, an den sie gebunden sind, einen Naphthalin- oder Tetrahydronaphthalinring bilden; R_1 Wasserstoff, eine Niederalkyl-, Aryl-, Aryl-Niederalkyl- oder Niederalkenylgruppe bedeutet; R_2 Wasserstoff, eine Niederalkyl-, Aryl-, Aryl-Niederalkyl-, (Niederalkyl-, Aryl-oder Aryl-Niederalkyl-)-thio- oder Niederalkenylgruppe bedeuten; oder R_1 und R_2 zusammen eine Niederalkyliden- oder C_4-C_6-Alkylengruppe bedeuten; und W die in Anspruch 1 angeführte Bedeutung aufweist; und Aryl im Rahmen der vorstehenden Definitionen eine Phenylgruppe oder eine durch einen oder zwei der folgenden Substituenten substituierte Phenylgruppe bedeutet: Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Nitro-, Aminogruppe, Halogen, Trifluormethyl-, Cyano-, Carboxy-, Niederalkoxycarbonyl-, Carbamoyl-, N-Niederalkylcarbamoyl- und N,N-Di-Niederalkylcarbamoyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Sulfamoyl-, N-Niederalkylsulfamoyl- oder N,N-Di-Niederalkylsulfamoylgruppe; oder einen heterocyclischen, aromatischen Rest bedeutet, wie einen Thienyl-, Indolyl-, Pyridyl- und Furylrest, oder einen dieser heterocyclischen Reste, die durch eine Niederalkyl-, Niederalkoxy-, Cyanogruppe oder Halogen monosubstituiert

sind, sowie pharmazeutisch verträgliche Salze davon.

3. Verwendung nach Anspruch 2 einer Verbindung der Formel (I), in der R_1 Wasserstoff bedeutet und W, R, R_0, R_2 sowie R_1 und R_2 zusammen die Bedeutung gemäß Anspruch 2 aufweisen.

4. Verbindungen der Formel (I)



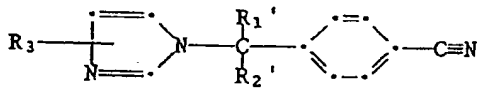
(I),

in der R und R_0 unabhängig voneinander Wasserstoff oder eine Niederalkylgruppe bedeuten; oder R und R_0 an benachbarten Kohlenstoffatomen und zusammen mit dem Benzolring, an den sie gebunden sind, einen Naphthalin- oder Tetrahydronaphthalinring bilden, R_1 Wasserstoff bedeutet, R_2 Wasserstoff, eine Niederalkyl-, Niederalkenyl-, Aryl-, Aryl-Niederalkyl-, C_3-C_6-Cycloalkyl- oder C_3-C_6-Cycloalkyl-Niederalkylgruppe bedeutet; oder R_1 und R_2 zusammen eine Niederalkyliden- oder Mono- oder Diaryl-Niederalkylidengruppe bedeuten; R_1 und R_2 zusammen auch eine C_4-C_6-geradkettige Alkylenkette, durch Niederalkylgruppen substituierte geradkettige Alkylengruppe oder eine orthoPhenylengruppe mit einer C_2-C_4-geradkettigen Alkylenbrücke bedeuten, so daß zusammen mit dem daran gebundenen Kohlenstoffatom ein entsprechender, gegebenenfalls substituierter oder Benzol-kondensierter 5-, 6- oder 7-gliedriger Ring gebildet wird; W eine 1-Imidazolyl, 1-(1,2,4- oder 1,3,4)-Triazolyl- oder 3-Pyridylgruppe darstellt; oder W eine durch Niederalkylgruppen substituierte 1-Imidazolyl-, 1-(1,2,4- oder 1,3,4-)-Triazolyl- oder 3-Pyridylgruppe bedeutet; und in den vorstehend genannten Definitionen Aryl Phenyl, gegebenenfalls substituert mit ein oder zwei Substituenten, ausgewählt aus Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Aroyloxy-, Niederalkoxycarbonyloxy-, N,N-Di-Niederalkylcarbamoyloxy-, Nitro-, Amino-, Halogen-, Trifluormethyl-, Cyano-, Carboxy-, Niederalkoxycarbonyl, (Phenyl-, Naphthyl-, Pyridyl-, Thienyl-, Indolyl- oder Furyl-)-Niederalkoxycarbonyl-,Niederalkanoyl-Niederalkoxycarbonyl-, 3-Phthalidoxycarbonyl-, Carbamoyl-, N-Niederalkylcarbamoyl-, N,N-Di-Niederalkylcarbamoyl-, Niederalkanoyl-, Aroyl-, Niederalkylsulfonyl-, Sulfamoyl-, N-Niederalkylsulfamoyl- und N,N-Di-Niederalkylsulfamoylgruppen; 1- oder 2-Naphthylgruppen, gegebenenfalls substituiert mit Niederalkyl-, Niederalkoxy-, Cyano- oder Halogengruppen; einen heterocyclischen aromatischen Rest, ausgewählt aus Thienyl-, Indolyl-, Pyridyl-, und Furylgruppen, oder der heterocyclische aromatische Rest monosubstituiert ist mit Niederalkyl-, Niederalkoxy-, Cyano- oder Halogengruppen bedeutet; und Aroyl in den vorstehenden Definitionen eine Benzoylgruppe, gegebenenfalls substituiert mit 1 oder 2 Niederalkyl-, Niederalkoxy-, Halogen- oder Trifluormethylgruppen; Thienoyl-, Pyrroloyl-, oder 2-, 3- oder 4-Pyridylcarbonylgruppen; bedeutet und Reste, die mit "Nieder" bezeichnet werden bis zu und einschließlich 7 Kohlenstoffatome enthalten, sowie pharmazeutisch verträgliche Salze davon.

5. Verbindungen nach Anspruch 4 der Formel (I), in denen R und R_0 Wasserstoff bedeuten; oder R und R_0 an benachbarten Kohlenstoffatomen und zusammen mit dem Benzolring, an den sie gebunden sind, einen Naphthalinring bilden; R_1 Wasserstoff bedeutet, R_2 Wasserstoff, eine Niederalkyl-, Aryl- oder Aryl-Niederalkylgruppe bedeutet; oder R_1 und R_2 zusammen eine Niederalkylidengruppe oder eine Diaryl-Niederalkylidengruppe bedeuten; R_1 und R_2 zusammen auch eine geradkettige C_4-C_6-Alkylengruppe oder eine ortho-Phenylengruppe mit einer geradkettigen C_2-C_4-Brücke darstellen, so daß sie zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen entsprechend substituierten oder gegebenenfalls Benzol-kondensierten 5-, 6- oder 7-gliedrigen Ring bilden; W einen 1-Imidazolyl-, 1-(1,2,4- oder 1,3,4-)-Triazolyl-, 3-Pyridyl- oder einen durch Niederalkylgruppen substituierten 1-Imidazolylrest bedeutet; und Aryl innerhalb der vorstehend gegebenen Definitionen eine Phenylgruppe oder eine durch Niederalkyl-, Niederalkoxy-, Hydroxy-, Halogen-, Trifluormethyl- oder Cyanogruppen substituierte Phenylgruppe; eine Thienyl- oder Pyridylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

6. Verbindungen nach Anspruch 4 der Formel (I), in denen R und R_0 unabhängig voneinander Wasserstoff oder Niederalkylgruppen bedeuten; oder R und R_0, die an benachbarten Kohlenstoffatomen stehen, zusammen und mit dem Benzolring, an den sie gebunden sind, einen Naphthalin- oder Tetrahydronaphthalinring bilden; R_1 Wasserstoff bedeutet; R_2 Wasserstoff, eine Niederalkyl-, Niederalkenyl-, Aryl- oder durch Niederalkylgruppen substituierte Arylgruppe bedeutet; oder R_1 und R_2 zusammen eine Niederalkyliden- oder C_4-C_6-Alkylengruppe bedeuten; W eine 1-Imidazolyl- oder eine durch Niederalkylgruppen substituierte 1-Imidazolylgruppe bedeutet; und Aryl innerhalb der vorstehenden Definitionen eine Phenylgruppe oder eine durch ein oder zwei der folgenden Substituenten substituierte Phenylgruppe bedeutet: Niederalkylgruppen, Niederalkoxygruppen, Hydroxy-, Niederalkanoyloxy-, Nitro-, Aminogruppen, Halogene, Trifluormethyl-, Cyano-, Carboxygruppen, Niederalkoxycarbonyl-, Carbamoyl-, N-Niederalkylcarbamoyl-, N,N-Di-Niederalkylcarbamoyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Sulfamoyl-, N-Niederalkylsulfamoyl- oder N,N-Di-Niederalkylsulfamoylgruppe; oder Aryl bedeutet in den vorstehend genannten Definitionen auch eine heterocyclische, aromatische Gruppe bedeutet, wie eine Thienyl-, Indolyl-, Pyridyl- oder Furylgruppe, oder eine der heterocyclischen Gruppen, die durch Niederalkyl-, Niederalkoxy-, Cyanogruppen oder Halogen monosubstituiert ist; sowie pharmazeutisch verträgliche Salze davon.

7. Verbindungen nach Anspruch 4 der Formel (II)



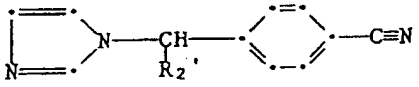
(II)

worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl-, Phenyl-, Pyridyl-, Thienyl- oder Benzylgruppe darstellt; oder R_2' eine Phenyl- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Benzoyloxy-, Nitro-, Trifluormethylgruppe, Halogen, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl- Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe substituiert sind; oder R_1' und R_2' zusammen eine Niederalkyliden-, Benzyliden- oder Diphenylmethylidengruppe bilden; oder R_1' und R_2' zusammen eine geradkettige C_4-C_6-Alkylenkette bedeuten; R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

8. Verbindungen nach Anspruch 7 der Formel (II), worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl-, Pyridyl-, Benzyl- oder Phenylgruppe darstellt; oder R_2' eine Benzyl- oder Phenylgruppe bedeutet, die jeweils am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxygruppe, Halogen, Nitro-, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe monosubstituiert sind; wobei R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

9. Verbindungen nach Anspruch 7 der Formel (II), in denen R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl-, Benzyl-, Phenyl- oder 3- oder 4-Pyridylgruppe bedeutet; oder R_2' eine Phenyl- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch Cyanogruppen, Halogene, eine Niederalkoxy-, Niederalkyl-, oder Trifluormethylgruppe monosubstituiert sind; R_3 Wasserstoff oder eine Niederalkylgruppe in der 4- oder 5-Position bedeutet; sowie pharmazeutisch verträgliche Salze davon.

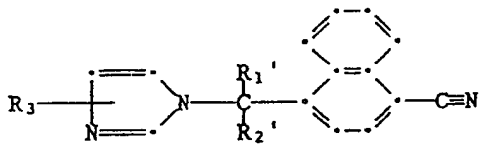
10. Verbindungen nach Anspruch 4 der Formel (III)



(III)

worin R_2' eine 3-Pyridyl-, p-Cyanobenzyl- oder p-Cyanophenylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

11. Verbindungen der Formel (IV)



(IV)

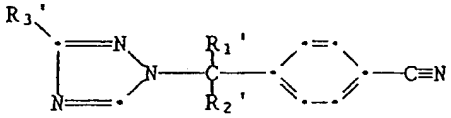
worin R_1' Wasserstoff darstellt; R_2' Wasserstoff, Niederalkylgruppen, Phenyl-, Niederalkylthio-, durch niedere Alkylthiogruppen substituierte Phenyl-, Phenylthio-, Pyridyl-, Thienyl- oder Benzylgruppen bedeutet; oder R_2' eine Phenyl; durch Niederalkylthiogruppen substituierte Phenyl-, Phenylthio- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Benzoyloxy-, Nitrogruppe, Halogen, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe monosubstituiert ist; oder R_1' und R_2' zusammen eine Niederalkyliden-, Benzyliden- oder Diphenylmethylidengruppe bedeuten, oder R_1' und R_2' zusammengenommen eine geradkettige C_4-C_6-Alkylenkette darstellen; R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

12. Verbindungen nach Anspruch 4 und 11 der Formel (IV), worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkylgruppe oder eine Pyridylgruppe bedeutet; oder R_2' eine Benzyl- oder Phenylgruppe bedeutet, die jeweils unsubstituiert oder am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxygruppe, Halogen, Nitro-, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe monosubstituiert ist; R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

13. Verbindungen nach Anspruch 12 der Formel (IV), worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl-, Benzyl-, Phenyl- oder 3- oder 4-Pyridylgruppe bedeutet; oder R_2' eine Phenyl- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch Halogen, eine Cyano-, Niederalkoxy-, Niederalkyl- oder Trifluormethylgruppe monosubstituiert ist; R_3 Wasserstoff oder eine Niederalkylgruppe an der 4- oder 5-Stellung bedeutet; sowie pharmazeutisch verträgliche Salze davon.

14. Verbindungen nach Anspruch 12 der Formel (IV), worin R_1' und R_3 ein Wasserstoffatom bedeuten; R_2' eine 3-Pyridyl-, p-Cyanobenzyl- oder p-Cyanophenylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

15. Verbindungen nach Anspruch 4 der Formel (V)



(V),

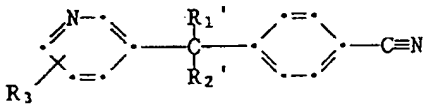
worin R_1' Wasserstoff bedeutet, R_2' Wasserstoff, eine Niederalkyl-, Phenyl-, Pyridyl-, Thienyl- oder Benzylgruppe bedeutet; oder R_2' eine Phenyl- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Benzoyloxy-, Nitro-, Trifluormethylgruppe, Halogen, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe monosubstituiert sind, oder R_1' und R_2' zusammen eine Niederalkyliden-, Benzyliden- oder Diphenylmethylidengruppe bedeuten, oder R_1' und R_2' zusammen eine geradkettige C_4-C_6-Alkylengruppe, R_3' Wasserstoff oder eine Niederalkylgruppe bedeuten; sowie pharmazeutisch verträgliche Salze davon.

16. Verbindungen nach Anspruch 15 der Formel (V), in denen R_1' Wasserstoff bedeutet, R_2' Wasserstoff, eine Niederalkyl-, eine Benzyl- oder Phenyl- oder 3- oder 4-Pyridylgruppe bedeutet; oder R_2' bedeutet eine Phenyl- oder Benzylgruppe, die jeweils am Phenylring durch eine Cyano-, Halogen, Niederalkoxy-,

Niederalkyl- oder Trifluormethylgruppe monosubstituiert ist; R_3' Wasserstoff oder eine Niederalkylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

17. Verbindungen nach Anspruch 15 der Formel (V), in denen R_1' und R_3' Wasserstoff darstellen, R_2' eine 3-Pyridyl-, p-Cyanobenzyl- oder p-Cyanophenylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

18. Verbindungen der Formel (VI)



(VI),

worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl-, Phenyl-, Niederalkylthio-, durch Niederalkylthiogruppe substituierte Phenyl-, Phenylthio-, Pydridyl-, Thienyl- oder Benzylgruppe bedeutet; oder R_2' eine Phenyl-, eine durch Niederalkylthiogruppen substituierte Phenyl-, Phenylthio- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Benzoyloxy-, Nitrogruppe, Halogen, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl, N-Mono- oder N,N-Di-Niedersulfamoylgruppe substituiert ist; oder R_1' und R_2' zusammen eine Niederalkyliden-, Benzyliden- oder Diphenylmethylidengruppe bedeuten;, oder R_1' und R_2' zusammen eine geradkettige C_4-C_6-Alkylengruppe bedeuten, R_3 Wasserstoff oder eine Niederalkylgruppe darstellt; sowie pharmazeutisch verträgliche Salze davon.

19. Verbindungen nach den Ansprüchen 4 und 18 der Formel (VI), worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl- oder Pyridylgruppe darstellt; oder R_2' eine Benzyl- oder Phenylgruppe bedeutet, die jeweils unsubstituiert oder durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoylgruppe, Halogen, Nitro-, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe am Phenylring monosubstituiert ist, R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet, sowie pharmazeutisch verträgliche Salze davon.

20. Verbindungen nach Anspruch 19 der Formel (VI), worin R_1' und R_3 Wasserstoff bedeuten; R_2' Wasserstoff, eine Niederalkyl-, Benzyl-, Phenyl- oder 3- oder 4-Pyridylgruppe bedeutet; oder R_2' eine Phenyl- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch Halogen, eine Cyano-, Niederalkoxy-, Niederalkyl- oder Trifluormethylgruppe monosubstituiert ist, sowie pharmazeutisch verträgliche Salze davon.

21. Verbindungen nach Anspruch 19 der Formel (VI), in der R_1' und R_3 Wasserstoff darstellen, R_2' eine 3- oder 4-Pyridyl-, p-Cyanobenzyl- oder p-Cyanophenylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

22. Verbindung nach Anspruch 4, nämlich 4-(α-Isopropyl-1-imidazolylmethyl)-benzonitril, ein Stereoisomer oder ein Gemisch von Stereoisomeren davon oder ein pharmazeutisch verträgliches Salz davon.

23. Verbindung nach Anspruch 4, nämlich 4-[α-(3-Pyridyl)-1-imidazolylmethyl]-benzonitril, ein Stereoisomer oder ein Gemisch von Stereoisomeren davon oder ein pharmazeutisch verträgliches Salz davon.

24. Verbindung nach Anspruch 4, nämlich 4-[α-(4-Cyanophenyl)-1-imidazolylmethyl]-benzonitril oder ein pharmazeutisch verträgliches Salz davon.

25. Verbindung nach Anspruch 4, nämlich 4-(α-Benzyl-1-imidazolylmethyl)-benzonitril, ein Stereoisomer oder ein Gemisch von Stereoisomeren davon oder ein pharmazeutisch verträgliches Salz davon.

26. Verbindung nach Anspruch 4, nämlich 2-(4-Cyanophenyl)-2-(1-imidazolyl)-indan oder ein pharmazeutisch verträgliches Salz davon.

27. Verbindung nach Anspruch 4, nämlich 4-[α-(4-Cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitril oder ein pharmazeutisch verträgliches Salz davon.

28. Arzneimittel, umfassend eine Verbindung nach einem der Ansprüche 4 bis 27 zusammen mit einem pharmazeutisch verträglichen Träger.

29. Verbindung nach einem der Ansprüche 4 bis 27 zur Verwendung bei einem Verfahren zur therapeutischen Behandlung des Körpers von Tier oder Mensch.

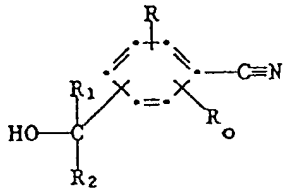
30. Verwendung einer Verbindung nach einem der Ansprüche 4 bis 27 zur Herstellung eines Arzneimittels zur Behandlung von für Inhibitoren der Aromataseaktivität empfängliche Zuständen.

31. Verfahren zur Herstellung von Verbindungen der Formel I nach Anspruch 4, oder Salzen davon, umfassend:

a) für Verbindungen der Formel (I), in denen W eine 1-Imidazolyl- oder 1-Triazolylgruppe bedeutet, die jeweils gegebenenfalls durch Niederalkylgruppen substituiert sein können, Kondensation einer Verbindung der Formel (VII)

W'- H (VII),

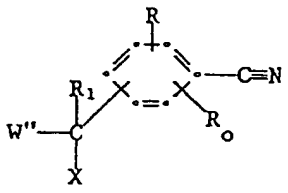
worin W' eine gegebenenfalls durch Niederalkylgruppen substituierte 1-Imidazolyl- oder 1-Triazolylgruppe bedeutet, oder ein N-geschütztes Derivat davon, mit einem reaktiven, veresterten Derivat einer Verbindung der Formel (VIII)



(VIII),

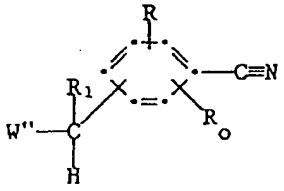
worin R, R_0, R_1 und R_2 die Bedeutung aufweisen, wie sie hierin für die Formel (I) bereits definiert worden ist;

b) für Verbindungen, in denen W eine gegebenenfalls durch Niederalkylgruppen substituierte 3-Pyridylgruppe bedeutet, Enthalogenierung einer Verbindung der Formel (IX)



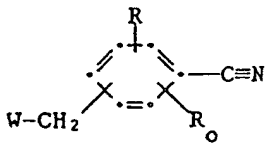
(IX)

worin W" eine gegebenenfalls durch Niederalkylgruppen substituierte 3-Pyridylgruppe bedeutet, X Halogen darstellt, vorzugsweise Chlor, R und R_0 die Bedeutung aufweisen, wie sie hierin bereits für Verbindungen der Formel (I) definiert worden ist; und R_1 die hier für Formel (I) definierte Bedeutung aufweist; und wenn notwendig, Umsetzung des so erhaltenen Produkts der Formel (X)



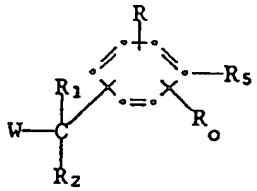
(X)

mit einem reaktiven Derivat des Restes R_2, wobei das Verfahren c) weiter unten verwendet wird.
c) Kondensation einer Verbindung der Formel (XI) unter basischen Bedingungen



(XI),

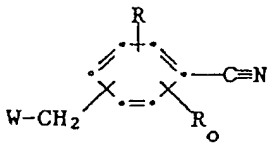
(die eine Verbindung der Formel (I) darstellt, worin R_1 und R_2 Wasserstoff bedeuten), R, R_0 und W die Bedeutung aufweisen, wie sie hierin für Formel (I) definiert worden ist, mit einem reaktiven, funktionellen Derivat eines Restes R_1 oder R_2 (wobei R_1 oder R_2 nicht Wasserstoff darstellen), wodurch eine Verbindung der Formel (I) erhalten wird, worin nur einer der beiden Reste R_1 und R_2 Wasserstoff bedeutet; oder Kondensation auf ähnliche Art einer Verbindung der Formel (I), die so erhalten worden ist, mit einem reaktiven, funktionellen Derivat eines Restes R_1 oder R_2 (wobei R_1 oder R_2 nicht Wasserstoff darstellen), wodurch eine Verbindung der Formel (I) erhalten wird, in der weder R_1 noch R_2 Wasserstoff bedeuten; oder Kondensation einer Verbindung der Formel (XI) mit einem reaktiven, difunktionellen Derivat von R_1 und R_2, die zusammen eine geradkettige C_4-C_6-Alkylengruppe, eine durch Niederalkylgruppen substituierte geradkettige C_4-C_6-Alkylengruppe oder eine 1,2-Phenylengruppe mit einer geradkettigen C_2-C_4-Alkylenbrücke bedeuten, zu einer entsprechenden Verbindung der Formel (I);
d) durch Umsetzung von R_5 in eine Cyanogruppe in einer Verbindung der Formel (XII)



(XII),

worin W, R, R_0, R_1 und R_2 vorstehende Bedeutung aufweisen und R_5 eine Gruppe oder einen Rest darstellt, der in die Cyanogruppe umgesetzt werden kann; und/oder Umsetzung einer Verbindung der Formel (I) in eine andere Verbindung der Formel (I); und/oder Umsetzung einer freien Verbindung in ein Salz, und/oder Umsetzung eines Salzes in eine freie Verbindung oder in ein anderes Salz; und/oder Trennung eines Gemisches von Isomeren oder Racematen in die einzelnen Isomere oder Racemate und/oder Auflösung eines Racemates in die optischen Isomeren.

32. Verfahren nach Anspruch 31 zur Herstellung einer Verbindung der Formel I, wobei R_1 Wasserstoff bedeutet; R_2 eine 4-Cyanophenylgruppe bedeutet; W, R und R_0 die Bedeutung gemäß vorstehendem Anspruch besitzen; umfassend die Kondensation unter basischen Bedingungen einer Verbindung der Formel XI



(XI)

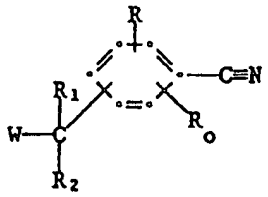
mit p-Fluorbenzonitril.

33. Verfahren nach Anspruch 32 zur Herstellung von 4-[α-(4-Cyanophenyl)-1-imidazolylmethyl]-benzonitril.

34. Verfahren nach Anspruch 32 zur Herstellung von 4-[α-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitril.

Patentanspruch für folgende Vertragsstaaten : AT, ES, GR

1. Verfahren zur Herstellung einer Verbindung der Formel I



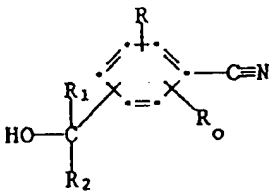
(I)

in der R und R_0 unabhängig voneinander Wasserstoff oder eine Niederalkylgruppe bedeuten; oder R und R_0 an benachbarten Kohlenstoffatomen und zusammen mit dem Benzolring, an den sie gebunden sind, einen Naphthalin- oder Tetrahydronaphthalinring bilden, R_1 Wasserstoff bedeutet, R_2 Wasserstoff, eine Niederalkyl-, Niederalkenyl-, Aryl-, Aryl-Niederalkyl-, C_3-C_6-Cycloalkyl- oder C_3-C_6-Cycloalkyl-Niederalkylgruppe bedeutet; oder R_1 und R_2 zusammen eine Niederalkyliden- oder Mono- oder Diaryl-Niederalkylidengruppe bedeuten; R_1 und R_2 zusammen auch eine C_4-C_6-geradkettige Alkylenkette, durch Niederalkylgruppen substituierte geradkettige Alkylengruppe oder eine orthoPhenylengruppe mit einer C_2-C_4-geradkettigen Alkylenbrücke bedeutet, so daß zusammen mit dem daran gebundenen Kohlenstoffatom ein entsprechender, gegebenenfalls substituierter oder Benzolkondensierter 5-, 6- oder 7-gliedriger Ring gebildet wird; W eine 1-Imidazolyl-, 1-(1,2,4- oder 1,3,4-)-Triazolyl- oder 3-Pyridylgruppe darstellt; oder W eine durch Niederalkylgruppen substituierte 1-Imidazolyl-, 1(1,2,4- oder 1,3,4-)-Triazolyl- oder 3-Pyridylgruppe bedeutet; und in den vorstehend genannten Definitionen Aryl Phenyl, gegebenenfalls substituiert mit ein oder zwei Substituenten, ausgewählt aus Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Aroyloxy-, Niederalkoxycarbonyloxy-, N,N-Di-Niederalkylcarbamoyloxy-, Nitro-, Amino-, Halogen-, Trifluormethyl-, Cyano-, Carboxy-, Niederalkoxycarbonyl, (Phenyl-, Naphthyl-, Pyridyl-, Thienyl-, Indolyl- oder Furyl-)-Niederalkoxycarbonyl-, Niederalkanoyl-Niederalkoxycarbonyl-, 3-Phthalidoxycarbonyl-, Carbamoyl-, N-Niederalkylcarbamoyl-, N,N-Di-Niederalkylcarbamoyl-, Niederalkanoyl-, Aroyl-, Niederalkylsulfonyl-, Sulfamoyl-, N-Niederalkylsulfamoyl- und N,N-Di-Niederalkylsulfamoylgruppen; 1- oder 2-Naphthylgruppen, gegebenenfalls substituiert mit Niederalkyl-, Niederalkoxy-, Cyano- oder Halogengruppen; einen heterocyclischen aromatischen Rest, ausgewählt aus Thienyl-, Indolyl-, Pyridyl- und Furylgruppen, oder der heterocyclische aromatische Rest monosubstituiert ist mit Niederalkyl-, Niederalkoxy-, Cyano- oder Halogengruppen bedeutet; und Aroyl in den vorstehenden Definitionen eine Benzoylgruppe, gegebenenfalls substituiert mit Niederalkyl-, Niederalkoxy-, Halogen- oder Trifluormethylgruppen; Thienoyl-, Pyrroloyl-, oder 2-, 3- oder 4-Pyridylcarbonylgruppen; bedeutet und Reste, die mit "Nieder" bezeichnet werden bis zu und einschließlich 7 Kohlenstoffatome enthalten, oder ein pharmazeutisch verträgliches Salz davon, umfassend

a) für Verbindungen der Formel (I), in denen W eine 1-Imidazolyl- oder 1-Triazolylgruppe bedeutet, die jeweils gegebenenfalls durch Niederalkylgruppen substituiert sein können, Kondensation einer Verbindung der Formel (VII)

W' - H (VII),

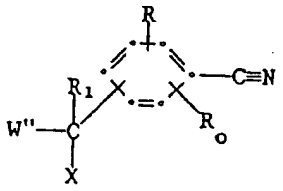
worin W' eine gegebenenfalls durch Niederalkylgruppen substituierte 1-Imidazolyl- oder 1-Triazolylgruppe bedeutet, oder ein N-geschütztes Derivat davon, mit einem reaktiven, veresterten Derivat einer Verbindung der Formel (VIII)



(VIII),

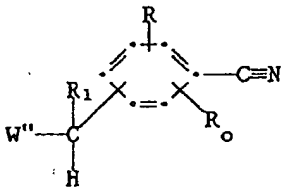
worin R, R_0, R_1 und R_2 die Bedeutung aufweisen, wie sie hierin für die Formel (I) bereits

definiert worden ist;
b) für Verbindungen, in denen W eine gegebenenfalls durch Niederalkylgruppen substituierte 3-Pyridylgruppe bedeutet, Enthalogenierung einer Verbindung der Formel (IX)



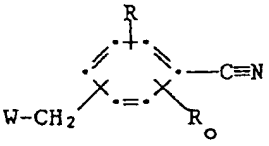
(IX)

worin W" eine gegebenenfalls durch Niederalkylgruppen substituierte 3-Pyridylgruppe bedeutet, X Halogen darstellt, vorzugsweise Chlor, R und R_0 die Bedeutung aufweisen, wie sie hierin bereits für Verbindungen der Formel (I) definiert worden ist und R_1 die hier für Formel (I) definierte Bedeutung besitzt; und wenn notwendig, Umsetzung des so erhaltenen Produkts der Formel (X)



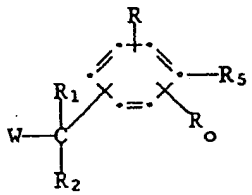
(X)

mit einem reaktiven Derivat des Restes R_2, wobei das Verfahren c) weiter unten verwendet wird.
c) Kondensation einer Verbindung der Formel (XI) unter basischen Bedingungen



(XI),

(die eine Verbindung der Formel (I) darstellt, worin R_1 und R_2 Wasserstoff bedeuten), worin R, R_0 und W die Bedeutung aufweisen, wie sie hierin für Formel (I) definiert worden ist, mit einem reaktiven, funktionellen Derivat eines Restes R_1 oder R_2 (wobei R_1 oder R_2 nicht Wasserstoff darstellen), wodurch eine Verbindung der Formel (I) erhalten wird, worin nur eine der beiden Gruppen R_1 und R_2 Wasserstoff bedeutet; oder Kondensation auf ähnliche Art einer Verbindung der Formel (I), die so erhalten worden ist, mit einem reaktiven, funktionellen Derivat eines Restes R_1 oder R_2 (wobei R_1 oder R_2 nicht Wasserstoff darstellen), wodurch eine Verbindung der Formel (I) erhalten wird, in der weder R_1 noch R_2 Wasserstoff bedeuten; oder Kondensation einer Verbindung der Formel (XI) mit einem reaktiven, difunktionellen Derivat von R_1 und R_2, die zusammen eine geradkettige C_4-C_6-Alkylengruppe, eine durch Niederalkylgruppen substituierte geradkettige C_4-C_6-Alkylengruppe oder eine 1,2-Phenylengruppe mit einer geradkettigen C_2-C_4-Alkylenbrücke bedeuten, zu einer entsprechenden Verbindung der Formel (I);
d) durch Umsetzung von R_5 in eine Cyanogruppe in einer Verbindung der Formel (XII)

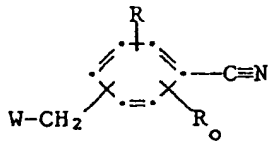


(XII),

worin W, R, R_0, R_1 und R_2 vorstehende Bedeutung aufweisen und R_5 eine Gruppe oder einen

Rest darstellt, das in die Cyanogruppe umgesetzt werden kann; und/oder Umsetzung einer Verbindung der Formel (I) in eine andere Verbindung der Formel (I); und/oder Umsetzung einer freien Verbindung in ein Salz, und/oder Umsetzung eines Salzes in eine freie Verbindung oder in ein anderes Salz; und/oder Trennung eines Gemisches von Isomeren oder Racematen in die einzelnen Isomere oder Racemate und/oder Auflösung eines Racemates in die optischen Isomeren.

2. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung nach Formel I, wobei R_1 Wasserstoff bedeutet; R_2 eine 4-Cyanophenylgruppe bedeutet; W, R und R_0 die Bedeutung gemäß vorstehendem Anspruch besitzen; umfassend die Kondensation unter basischen Bedingungen einer Verbindung der Formel XI



(XI)

mit p-Fluorbenzonitril.

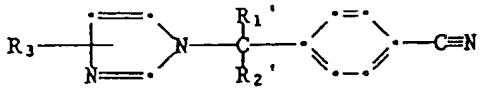
3. Verfahren nach Anspruch 2 zur Herstellung von 4-[α-(4-Cyanophenyl)-1-imidazolylmethyl]-benzonitril.

4. Verfahren nach Anspruch 2 zur Herstellung von 4-[α-(4-Cyanophenyl)-1-(1,2,4-triazolyl)methyl]-benzonitril.

5. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung nach Formel I, wobei R und R_0 Wasserstoff bedeuten; oder R und R_0 an benachbarten Kohlenstoffatomen und zusammen mit dem Benzolring, an den sie gebunden sind, einen Naphthalinring bilden, R_1 Wasserstoff bedeutet, R_2 Wasserstoff, eine Niederalkyl-, Aryl- oder Aryl-Niederalkylgruppe bedeutet oder R_1 und R_2 zusammen eine Nieder-Alkylidengruppe oder eine Diaryl-Niederalkylidengruppe bedeuten; R_1 und R_2 zusammen auch eine geradkettige C_4-C_6-Alkylengruppe oder eine ortho-Phenylengruppe mit einer geradkettigen C_2-C_4-Brücke darstellen, so daß sie zusammen mit dem Kohlenstoffatom, an das sie gebunden sind, einen entsprechend substituierten oder gegebenenfalls Benzol-kondensierten 5-, 6- oder 7-gliedrigen Ring bilden, W eine 1-Imidazolyl-, 1-(1,2,4- oder 1,3,4-)-Triazolyl-, 3-Pyridyl oder eine durch Niederalkylgruppen substituierte 1-Imidazolylgruppe bedeutet; und Aryl innerhalb der vorstehend gegebenen Definitionen eine Phenylgruppe oder eine durch Niederalkyl-, Niederalkoxy-, Hydroxy-, Trifluormethyl-, Cyanogruppen oder Halogen substituierte Phenylgruppe, eine Thienyl- oder Pyridylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

6. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung nach Formel I, wobei R und R_0 unabhängig voneinander Wasserstoff oder Niederalkylgruppen bedeuten; oder R und R_0, die an benachbarten Kohlenstoffatomen stehen und zusammen mit dem Benzolring, an den sie gebunden sind, einen Naphthalin- oder Tetrahydronaphthalinring bilden; R_1 Wasserstoff bedeutet; R_2 Wasserstoff, eine Niederalkyl-, Niederalkenyl-, Aryl- oder durch Niederalkylgruppen substituierte Arylgruppe bedeutet; oder R_1 und R_2 zusammen eine Niederalkyliden- oder C_4-C_6-Alkylengruppe bedeuten; W eine 1-Imidazolyl- oder eine durch Niederalkylgruppen substituierte 1-Imidazolylgruppe bedeutet, und Aryl innerhalb der vorstehenden Definitionen eine Phenylgruppe oder eine durch ein oder zwei der folgenden Substituenten substituierte Phenylgruppe bedeutet: Niederalkylgruppen, Niederalkoxygruppen, Hydroxy-, Niederalkanoyloxy-, Nitro-, Aminogruppen, Halogene, Trifluormethyl-, Cyano-, Carboxygruppen, Niederalkoxcarbonyl-, Carbamoyl-, N-Niederalkylcarbamoyl-, N,N-Di-Niederalkylcarbamoyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Sulfamoyl-, N-Niederalkylsulfamoyl- oder N,N-Di-Niederalkyl-sulfamoylgruppe oder Aryl bedeutet in den vorstehend genannten Definitionen auch eine heterocyclische, aromatische Gruppe wie eine Thienyl-, Indolyl-, Pyridyl- oder Furylgruppe, oder eine der Gruppen, die durch Niederalkyl-, Niederalkoxy-, Cyanogruppen oder Halogen monosubstituiert ist; sowie pharmazeutisch verträgliche Salze davon.

7. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (II) bevorzugt



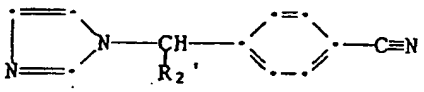
(II)

worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl-, Phenyl-, Pyridyl-, Thienyl- oder Benzylgruppe darstellt; oder R_2' eine Phenyl- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch eine Cyano-, Niederalkyl-, NiederalkoxyHydroxy-, Niederalkanoyloxy-, Benzoyloxy-, Nitro-, Trifluormethylgruppe, Halogen, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe substituiert sind; oder R_1' und R_2' zusammen eine Niederalkyliden-, Benzyliden- oder Diphenylmethylidengruppe bilden; oder R_1' und R_2' zusammen eine geradkettige C_4-C_6-Alkylenkette bedeuten; R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet, sowie pharmazeutisch verträgliche Salze davon.

8. Verfahren nach Anspruch 7 der Formel (II), worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl-, Pyridyl-, Benzyl- oder Phenylgruppe darstellt; oder R_2' eine Benzyl- oder Phenylgruppe bedeutet, die jeweils am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxygruppe, Halogen, Nitro-, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe monosubstituiert sind; wobei R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

9. Verfahren nach Anspruch 7 zur Herstellung einer Verbindung der Formel (II), wobei R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl-, Benzyl-, Phenyl- oder 3- oder 4-Pyridylgruppe bedeutet, oder R_2' eine Phenyl- oder Benzylgruppe bedeutet; die jeweils am Phenylring durch Cyanogruppen, Halogene, eine Niederalkoxy-, Niederalkyl-, oder Trifluormethylgruppe monosubstituiert sind; R_3 Wasserstoff oder eine Niederalkylgruppe in der 4- oder 5-Stellung bedeutet; sowie pharmazeutisch verträgliche Salze davon.

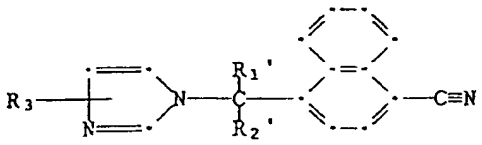
10. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (III)



(III)

worin R_2 eine 3-Pyridyl-, p-Cyanobenzyl- oder p-Cyanophenylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

11. Verfahren zur Herstellung einer Verbindung der Formel (IV)



(IV)

worin R_1' Wasserstoff darstellt; R_2' Wasserstoff, Niederalkylgruppen, Phenyl-, Niederalkylthio-, durch niedere Aklylthiogruppen substituierte Phenyl-, Phenylthio-, Pyridyl-, Thienyl- oder Benzylgruppen bedeutet; oder R_2' eine Phenyl, durch Niederalkylthiogruppen substituierte Phenyl-, Phenylthio- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch eine Cyan-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Benzoyloxy-, Nitrogruppe, Halogen, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkycarbamoyl-, Sulfamoyl-, N-Mono- oder N,N Di-Niederalkylsulfamoylgruppe monosubstituiert sind; oder R_1' und R_2' zusammen eine Niederalkyliden-, Benzyliden- oder Diphenylmethylidengruppe bedeuten, oder R_1' und R_2' zusam-

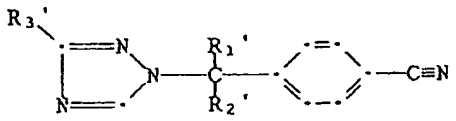
mengenommen eine geradkettige C_4-C_6-Alkylenkette darstellen; R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon, wobei das Verfahren gemäß einem der Verfahren a), c) oder d) nach Anspruch 1 ausgeführt wird unter Verwendung von Ausgangsmaterialien, die zum Erhalt von Verbindungen der Formel (IV) geeignete Substituenten tragen und/oder Umsetzung einer Verbindung der Formel (IV) in eine andere Verbindung der Formel (IV); und/oder Umsetzung einer freien Verbindung in ein Salz, und/oder Umsetzung eines Salzes in eine freie Verbindung oder in ein anderes Salz; und/oder Trennung eines Gemisches von Isomeren oder Racematen in die einzelnen Isomere oder Racemate und/oder Auflösung eines Racemates in die optischen Isomeren.

12. Verfahren nach Anspruch 11 zur Herstellung einer Verbindung der Formel (IV), worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkylgruppe oder eine Pyridylgruppe bedeutet; oder R_2' eine Benzyl- oder Phenylgruppe bedeutet, die jeweils unsubstituiert oder am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxygruppe, Halogen, Nitro-, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe monosubstituiert sind; R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

13. Verfahren nach Anspruch 12 zur Herstellung einer Verbindung der Formel (IV), worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl-, Benzyl-, Phenyl- oder 3- oder 4-Pyridylgruppe bedeutet; oder R_2' eine Phenyl- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch Halogen, eine Cyan-, Niederalkoxy-, Niederalkyl- oder Trifluormethylgruppe monosubstituiert sind; R_3 Wasserstoff oder eine Niederalkylgruppe an der 4- oder 5-Stellung bedeutet; sowie pharmazeutisch verträgliche Salze davon.

14. Verfahren nach Anspruch 12 zur Herstellung einer Verbindung der Formel (IV), worin R_1' und R_3 Wasserstoff bedeuten; R_2' 3-Pyridyl-, p-Cyanobenzyl- oder p-Cyanophenylgruppe bedeutet oder eines pharmazeutisch verträglichen Salzes davon.

15. Verfahren nach Anspruch 1 zur Herstellung einer Verbindung der Formel (V)



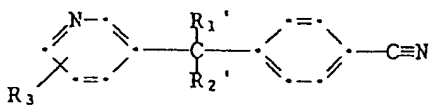
(V),

worin R_1' Wasserstoff bedeutet, R_2' Wasserstoff, eine Niederalkyl-, Phenyl-, Pyridyl-, Thienyl- oder Benzylgruppe bedeutet; oder R_2' eine Phenyl- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Benzoyloxy-, Nitro-, Trifluormethylgruppe, Halogen, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-, Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe monosubstituiert sind, oder R_1' und R_2' zusammen eine Niederalkyliden-, Benzyliden- oder Diphenylmethylidengruppe bedeuten, oder R_1' und R_2' zusammen eine geradkettige C_4-C_6-Alkylengruppe, R_3' Wasserstoff oder eine Niederalkylgruppe bedeuten; sowie pharmazeutisch verträgliche Salze davon.

16. Verfahren nach Anspruch 15 zur Herstellung einer Verbindung der Formel (V), wobei R_1' Wasserstoff bedeutet, R_2' Wasserstoff, eine Niederalkyl-, eine Benzyl- oder Phenylgruppe, oder 3- oder 4-Pyridylgruppe bedeutet, die jeweils unsubstituiert oder am Phenylring durch eine Cyano-, Halogen, Niederalkoxy-, Niederalkyl-, oder Trifluormethylgruppe ist, R_3' Wasserstoff oder eine Niederalkylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

17. Verfahren nach Anspruch 15 zur Herstellung einer Verbindung der Formel (V), wobei R_1' und R_3' Wasserstoff darstellen, R_2' eine 3-Pyridyl-, p-Cyanobenzyl- oder p-Cyanophenylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

18. Verfahren zur Herstellung einer Verbindung der Formel (VI)



(VI),

worin R_1' Wasserstoff bedeutet, R_2' Wasserstoff, eine Niederalkyl-, Phenyl-, Niederalkylthio-, durch Niederalkylthiogruppe substituierte Phenyl-, Phenylthio-, Pydridyl-, Thienyl- oder Benzylgruppe bedeutet, oder R_2' eine Phenyl-, eine durch Niederalkykllthiogruppe substituierte Phenyl-, Phenylthio- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoyloxy-, Benzoyloxy-, Nitrogruppe, Halogen, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-,Sulfamoyl, N-Mono- oder N,N-Di-Niedersulfamoylgruppe substituiert ist, oder R_1' und R_2' zusammen eine Niederalkyliden-, Benzyliden- oder Diphenylmethylidengruppe bedeuten, oder R_1' und R_2' zusammen eine geradkettige C_4-C_6-Alkylengruppe bedeuten, R_3 Wasserstoff oder eine Niederalkylgruppe darstellt; sowie pharmazeutisch verträgliche Salze davon, wobei das Verfahren gemäß einem der Verfahren a), b), c) oder d) nach Anspruch 1 ausgeführt wird unter Verwendung von Ausgangsmaterialien, die zum Erhalt von Verbindungen der Formel (VI) geeignete Substituenten tragen und/oder Umsetzung einer Verbindung der Formel (VI) in eine andere Verbindung der Formel (VI); und/oder Umsetzung einer freien Verbindung in ein Salz, und/oder Umsetzung eines Salzes in eine freie Verbindung oder in ein anderes Salz; und/oder Trennung eines Gemisches von Isomeren oder Racematen in die einzelnen Isomere oder Racemate und/oder Auflösung eines Racemates in die optischen Isomeren.

19. Verfahren nach Anspruch 18 zur Herstellung einer Verbindung der Formel (VI), worin R_1' Wasserstoff bedeutet; R_2' Wasserstoff, eine Niederalkyl- oder Pyridylgruppe darstellt oder R_2' eine Benzyl- oder Phenylgruppe bedeutet, die jeweils unsubstituiert oder durch eine Cyano-, Niederalkyl-, Niederalkoxy-, Hydroxy-, Niederalkanoylgruppe, Halogen, Nitro-, Trifluormethyl-, Niederalkanoyl-, Benzoyl-, Niederalkylsulfonyl-, Carbamoyl-, N-Mono- oder N,N-Di-Niederalkylcarbamoyl-,Sulfamoyl-, N-Mono- oder N,N-Di-Niederalkylsulfamoylgruppe am Phenylring monosubstituiert ist, R_3 Wasserstoff oder eine Niederalkylgruppe bedeutet, sowie pharmazeutisch verträgliche Salze davon.

20. Verfahren nach Anspruch 19 zur Herstellung einer Verbindung der Formel (VI), worin R_1' und R_3' Wasserstoff bedeuten; R_2' Wasserstoff, eine Niederalkyl-, Benzyl-, Phenyl- oder 3- oder 4-Pyridylgruppe bedeutet; oder R_2' eine Phenyl- oder Benzylgruppe bedeutet, die jeweils am Phenylring durch Halogen, eine Cyano-, Niederalkoxy-, Niederalkyl- oder Trifluormethylgruppe monosubstituiert ist; sowie pharmazeutisch verträgliche Salze davon.

21. Verfahren nach Anspruch 19 zur Herstellung einer Verbindung der Formel (VI), wobei R_1' und R_3' Wasserstoff darstellen, R_2' eine 3- oder 4-Pyridyl-, p-Cyanobenzyl- oder p-Cyanophenylgruppe bedeutet; sowie pharmazeutisch verträgliche Salze davon.

22. Verfahren nach Anspruch 1, **dadurch gekennzeichnet,** daß 4-(α-Isopropyl-1-imidazolylmethyl)-benzonitril, ein Stereoisomer oder ein Gemisch von Stereoisomeren davon oder ein pharmazeutisch verträgliches Salz davon, hergestellt wird.

23. Verfahren nach Anspruch 1, **dadurch gekennzeichnet,** daß 4-[α-(3-Pyridyl)-1-imidazolylmethyl]-benzonitril, ein Stereoisomer oder ein Gemisch von Stereoisomeren davon oder ein pharmazeutisch verträgliches Salz davon, hergestellt wird.

24. Verfahren nach Anspruch 1, **dadurch gekennzeichnet,** daß 4-[α-(Cyanophenyl)-1-imidazolylmethyl]-benzonitril, oder ein pharmazeutisch verträgliches Salz davon, hergestellt wird.

25. Verfahren nach Anspruch 1, **dadurch gekennzeichn t,** daß 4-(α-Benzyl-1-imidazolylmethyl)-benzonitril, ein Stereoisomer oder ein Gemisch von Stereoisomeren davon oder ein pharmazeutisch verträgliches Salz davon, hergestellt wird.

26. Verfahren nach Anspruch 1, **dadurch gek nnzeichnet,** daß 2-(4-Cyanophenyl)-2-(1-imidazolyl)indan, oder ein pharmazeutisch verträgliches Salz davon, hergestellt wird.

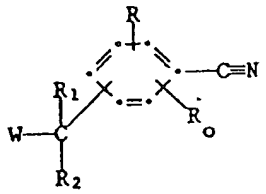
27. Verfahren nach Anspruch 1, **dadurch gekennzeichnet,** daß 4-[α-(4-Cyanophenyl)-1-(1,2,4-triazolyl)-methyl]-benzonitril, oder ein pharmazeutisch verträgliches Salz davon, hergestellt wird.

28. Verfahren zur Herstellung eines Arzneimittels, umfassend die Zugabe einer gemäß Ansprüchen 1-27 erhältlichen Verbindung in einem prozentualem Anteil von 1-50%.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Utilisation d'un composé de formule I



(I)

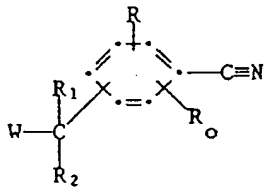
dans laquelle R et R_o représentent indépendamment un atome d'hydrogène ou un groupe alkyle inférieur; ou R et R_o, situés sur des atomes de carbone adjacents, forment ensemble, conjointement avec le cycle benzénique auquel ils sont liés, un cycle naphtalène ou tétrahydronaphtalène; R_1 et R_2 représentent indépendamment un atome d'hydrogène ou un groupe alkyle inférieur, (alkyl inférieur, aryl ou aryl-alkyl inférieur)-thio, alcényle inférieur, aryle, aryl-alkyle inférieur, cycloalkyle en C_3-C_6 ou cycloalkyl(C_3-C_6)-alkyle inférieur; ou R_1 et R_2 représentent ensemble un groupe alkylidène inférieur, mono- ou diaryl-alkylidène inférieur; R_1 et R_2 ensemble représentent également un groupe alkylène à chaîne droite en C_4-C_6, alkylène à chaîne droite substitué par un radical alkyle inférieur, ou un groupe alkylène à chaîne droite en C_2-C_4 pontée par un radical o-phénylène, formant chacun, avec l'atome de carbone auquel il est lié, un cycle à 5, 6 ou 7 chaînons correspondant, éventuellement substitué ou soudé à un noyau benzénique; W représente le groupe 1-imidazolyle, 1-(1,2,4- ou -1,3,4)-triazolyle ou 3-pyridyle; ou W représente un groupe 1-imidazolyle, 1-(1,2,4- ou -1,3,4)-triazolyle ou 3-pyridyle substitué par un radical alkyle inférieur;
et "aryle" dans les définitions ci-dessus représente un groupe phényle qui est non substitué ou substitué par un ou deux substituants choisis parmi des atomes d'halogène et des groupes alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, aroyloxy, (alcoxy inférieur)-carbonyloxy, N,N-di(alkyl inférieur)-carbamoyloxy, nitro, amino, trifluorométhyle, cyano, carboxy, (alcoxy inférieur)-carbonyle, (phényl, naphtyl, pyridyl, thiényl, indolyl ou furyl)-(alcoxy inférieur)-carbonyle, alcanoyloxy inférieur(alcoxy inférieur)-carbonyle, 3-phtalidoxycarbonyle, carbamoyle, N-(alkyl inférieur)-carbamoyle, N,N-di(alkyl inférieur)-carbamoyle, alcanoyle inférieur, aroyle, (alkyl inférieur)-sulfonyle, sulfamoyle, N-(alkyl inférieur)-sulfamoyle et N,N-di(alkyl inférieur)-sulfamoyle; un groupe 1- ou 2-naphtyle qui est non substitué ou substitué par des substituants halogène, alkyle inférieur, alcoxy inférieur ou cyano; un radical aromatique hétérocyclique choisi parmi les radicaux thiényle, indolyle, pyridyle et furyle; ou un tel radical aromatique hétérocyclique qui est monosubstitué par un atome d'halogène ou par un groupe alkyle inférieur, alcoxy inférieur ou cyano;
et "aroyle" dans les définitions ci-dessus représente un radical benzoyle qui est non substitué ou substitué par 1 ou 2 atomes d'halogène ou groupes alkyle inférieur, alcoxy inférieur ou trifluorométhyle; le radical thiénoyle, pyrroloyle ou 2-, 3- ou 4-pyridylcarbonyle;
et les radicaux désignés comme "inférieurs" contiennent jusqu'à et y compris 7 atomes de carbone;
ou de ses sels pharmaceutiquement acceptables, pour la préparation d'une composition pharmaceutique pour le traitement de maladies répondant à l'inhibition de l'aromatase.

2. Utilisation selon la revendication 1 d'un composé de formule I dans lequel R et R_o représentent indépendamment un atome d'hydrogène ou un groupe alkyle inférieur; ou R et R_o, situés sur des atomes de carbone adjacents, forment ensemble, conjointement avec le noyau benzénique auquel ils sont liés, un cycle naphtalène ou tétrahydronaphtalène; R_1 représente un atome d'hydrogène ou un

groupe alkyle inférieur, aryle, aryl-alkyle inférieur ou alcényle inférieur, R_2 représente un atome d'hydrogène ou un groupe alkyle inférieur, aryle, aryl-alkyle inférieur, (alkyl inférieur, aryl ou aryl-alkyl inférieur)-thio ou alcényle inférieur; ou R_1 et R_2 représentent ensemble un groupe alkylidène inférieur ou alkylène en C_4-C_6; W a la signification donnée dans la revendication 1; et "aryle" dans les définitions ci-dessus représente le groupe phényle ou un groupe phényle substitué par un ou deux substituants choisis parmi des atomes d'halogène et des groupes alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, nitro, amino, trifluorométhyle, cyano, carboxy, (alcoxy inférieur)-carbonyle, carbamoyle, N-(alkyl inférieur)-carbamoyle, N,N-di(alkyl inférieur)-carbamoyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, sulfamoyle, N-(alkyl inférieur)-sulfamoyle ou N,N-di(alkyl inférieur)-sulfamoyle; ou un radical aromatique hétérocyclique choisi parmi les radicaux thiényle, indolyle, pyridyle et furyle; ou un tel radical hétérocyclique monosubstitué par un atome d'halogène ou un groupe alkyle inférieur, alcoxy inférieur ou cyano; ou d'un sel pharmaceutiquement acceptable de celui-ci.

3. Utilisation selon la revendication 2 d'un composé de formule I dans lequel R_1 représente un atome d'hydrogène et W, R, R_0, R_2 ainsi que R_1 et R_2 réunis ont les significations données dans la revendication 2.

4. Composés de formule I



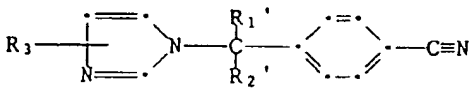
(I)

dans laquelle R et R_0 représentent indépendamment un atome d'hydrogène ou un groupe alkyle inférieur; ou R et R_0, situés sur des atomes de carbone adjacents, forment ensemble, conjointement avec le noyau benzénique auquel ils sont liés, un cycle naphtalène ou tétrahydronaphtalène; R_1 représente un atome d'hydrogène; R_2 représente un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur, aryle, aryl-alkyle inférieur, cycloalkyle en C_3-C_6 ou cycloalkyl(C_3-C_6)-alkyle inférieur; ou R_1 et R_2 représentent ensemble un groupe alkylidène inférieur ou mono- ou diarylalkylidène inférieur; R_1 et R_2 réunis représentent également un groupe alkylène à chaîne droite en C_4-C_5, alkylène à chaine droite substitué par un groupe alkyle inférieur, ou alkylène à chaîne droite en C_2-C_4 pontée par un groupe o-phénylène, pour former, avec l'atome de carbone auquel ils sont liés, un cycle à 5, 6 ou 7 chaînons correspondant, éventuellement substitué ou soudé à un noyau benzénique, W représente le radical 1-imidazolyle, 1-(1,2,4- ou -1,3,4)-triazolyle ou 3-pyridyle; ou W représente un groupe 1-imidazolyle, 1-(1,2,4- ou -1,3,4)-triazolyle ou 3-pyridyle substitué par un radical alkyle inférieur; et, dans les définitions ci-dessus, un groupe aryle représente un groupe phényle qui est non substitué ou substitué par un ou deux substituants choisis parmi des atomes d'halogène et des groupes alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, aroyloxy, (alcoxy inférieur)-carbonyloxy, N,N-di(alkyl inférieur)-carbamoyloxy, nitro, amino, trifluorométhyle, cyano, carboxy, (alcoxy inférieur)carbonyle, (phényl, naphtyl, pyridyl, thiényl, indolyl ou furyl)-(alcoxy inférieur)-carbonyle, (alcanoyloxy inférieur)-(alcoxy inférieur)-carbonyle, 3-phtalidoxycarbonyle, carbamoyle, N-(alkyl inférieur)-carbamoyle, N,N-di(alkyl inférieur)-carbamoyle, alcanoyle inférieur, aroyle, (alkyl inférieur)-sulfonyle, sulfamoyle, N-(alkyl inférieur)-sulfamoyle et N,N-di(alkyl inférieur)-sulfamoyle; un groupe 1- ou 2-naphtyle qui est non substitué ou substitué par un groupe alkyle inférieur, alcoxy inférieur, cyano ou par un atome d'halogène; un radical aromatique hétérocyclique choisi parmi les radicaux thiényle, indolyle, pyridyle et furyle; ou un tel radical aromatique hétérocyclique qui est monosubstitué par un atome d'halogène ou par un groupe alkyle inférieur, alcoxy inférieur ou cyano; et "aroyle" dans les définitions ci-dessus représente un groupe benzoyle qui est non substitué ou substitué par un ou deux substituants halogène, alkyle inférieur, alcoxy inférieur ou trifluorométhyle; le groupe thiénoyle, pyrroloyle ou 2-, 3- ou 4-pyridylcarbonyle;
et les radicaux désignés par "inférieurs" contiennent jusqu'à et y compris 7 atomes de carbone;
et sels pharmaceutiquement acceptables de ceux-ci.

5. Composés selon la revendication 4, de formule I, dans lesquels R et R_0 représentent un atome d'hydrogène; ou R et R_0, situés sur des atomes de carbone adjacents, forment ensemble, conjointement avec le noyau benzénique auquel ils sont liés, un cycle naphtalène; R_1 représente un atome d'hydrogène; R_2 représente un atome d'hydrogène ou un groupe alkyle inférieur, aryle ou aryl-alkyle inférieur; ou R_1 et R_2 réunis représentent ensemble un groupe alkylidène inférieur ou diaryl-alkylidène inférieur; R_1 et R_2 réunis peuvent également représenter un groupe alkylène à chaîne droite en C_4-C_6 ou alkylène à chaîne droite en C_2-C_4 pontée par un radical o-phénylène, pour former, avec l'atome de carbone auquel ils sont liés, un cycle à 5, 6 ou 7 chaînons correspondant, éventuellement soudé à un noyau bénzénique; W représente le groupe 1-imidazoyle, 1-(1,2,4- ou -1,3,4)-triazolyle, 3-pyridyle ou un groupe 1-imidazolyle substitué par un groupe alkyle inférieur; et "aryle" dans les définitions ci-dessus représente le radical phényle ou un radical phényle substitué par un atome d'halogène et par un groupe alkyle inférieur, alcoxy inférieur, hydroxy, trifluorométhyle ou cyano; le radical thiényle ou pyridyle; et sels pharmaceutiquement acceptables de ceux-ci.

6. Composés selon la revendication 4, de formule I, dans lesquels R et R_0 représentent indépendamment un atome d'hydrogène ou un groupe alkyle inférieur; ou R et R_0, situés sur des atomes de carbone adjacents, forment ensemble, conjointement avec le noyau benzénique auquel ils sont liés, un cycle naphtalène ou tétrahydronaphtalène; R_1 représente un atome d'hydrogène; R_2 représente un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur, aryle ou aryl-alkyle inférieur; ou R_1 et R_2 réunis représentent ensemble un groupe alkylidène inférieur ou alkylène en C_4-C_6; W représente un groupe 1-imidazolyle, ou 1-imidazolyle substitué par un radical alkyle inférieur; et "aryle" dans les définitions ci-dessus représente le radical phényle ou un radical phényle substitué par un ou deux substituants choisis parmi des atomes d'halogène et des groupes alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, nitro, amino, trifluorométhyle, cyano, carboxy, (alcoxy inférieur)-carbonyle, carbamoyle, N-(alkyl inférieur)-carbamoyle, N,N-di(alkyl inférieur)-carbamoyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, sulfamoyle, N-(alkyl inférieur)-sulfamoyle ou N,N-di(alkyl inférieur)-sulfamoyle; ou "aryle" dans les définitions ci-dessus représente également un radical aromatique hétérocyclique choisi parmi les radicaux thiényle, indolyle, pyridyle et furyle, ou un tel radical hétérocyclique monosubstitué par un atome d'halogène ou par un groupe alkyle inférieur, alcoxy inférieur ou cyano; et sels pharmaceutiquement acceptables de ceux-ci.

7. Composés selon la revendication 4, de formule II



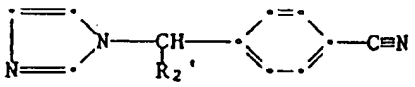
(II)

dans laquelle R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, phényle, pyridyle, thiényle ou benzyle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, benzoyloxy, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; ou R_1' et R_2' réunis représentent ensemble un groupe alkylidène inférieur, benzylidène ou diphénylméthylidène; ou R_1' et R_2' réunis représentent ensemble un groupe alkylène à chaîne droite en C_4-C_6; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; et sels pharmaceutiquement acceptables de ceux-ci.

8. Composés selon la revendication 7, de formule II, dans lesquels R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, pyridyle, benzyle ou phényle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; et sels pharmaceutiquement acceptables de ceux-ci.

9. Composés selon la revendication 7, de formule II, dans lesquels R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, benzyle, phényle ou 3- ou 4-pyridyle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alcoxy inférieur, alkyle inférieur ou trifluorométhyle; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur en position 4 ou 5; et sels pharmaceutiquement acceptables de ceux-ci.

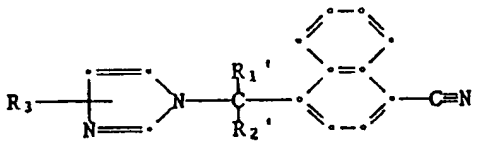
10. Composés selon la revendication 4, de formule III



(III)

dans laquelle R_2' représente le groupe 3-pyridyle, p-cyanobenzyle ou p-cyanophényle; et sels pharmaceutiquement acceptables de ceux-ci.

11. Composés de formule IV



(IV)

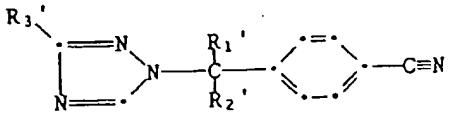
dans laquelle R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, phényle, (alkyl inférieur)-thio, phényl-(alkyl inférieur)-thio, phénylthio, pyridyle, thiényle ou benzyle; ou R_2' représente un radical phényle, phényl-(alkyl inférieur)-thio, phénylthio ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, benzoyloxy, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; ou R_1' et R_2' réunis représentent ensemble un groupe alkylidène inférieur, benzylidène, diphénylméthylidène; ou R_1' et R_2' réunis représentent ensemble un groupe alkylène à chaîne droite en C_4-C_6; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; et sels pharmaceutiquement acceptables de ceux-ci.

12. Composés selon les revendications 4 et 11, de formule IV, dans lesquels R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur ou pyridyle; ou R_2' représente un groupe benzyle ou phényle, chacun non substitué ou monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; et sels pharmaceutiquement acceptables de ceux-ci.

13. Composés selon la revendication 12, de formule IV, dans lesquels R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, benzyle, phényle ou 3- ou 4-pyridyle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alcoxy inférieur, alkyle inférieur ou trifluorométhyle; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur en position 4 ou 5; et sels pharmaceutiquement acceptables de ceux-ci.

14. Composés selon la revendication 12, de formule IV, dans lesquels R_1' et R_3 représentent un atome d'hydrogène; R_2' représente le groupe 3-pyridyle, p-cyanobenzyle ou p-cyanophényle; et leurs sels pharmaceutiquement acceptables.

15. Composés selon la revendication 4, de formule V



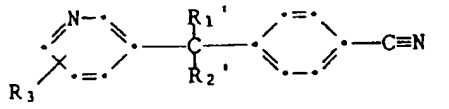
(V)

dans laquelle R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, phényle, pyridyle, thiényle ou benzyle ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le noyau phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, benzoyloxy, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; ou R_1' et R_2' réunis représentent ensemble un groupe alkylidène inférieur, benzylidène ou diphénylméthylidène; ou R_1' et R_2' réunis représentent ensemble un groupe alkylène à chaîne droite en C_4-C_6; R_3' représente un atome d'hydrogène ou un groupe alkyle inférieur; et leurs sels pharmaceutiquement acceptables.

16. Composés selon la revendication 15, de formule V, dans lesquels R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, benzyle, phényle ou 3- ou 4-pyridyle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou un groupe cyano, alcoxy inférieur, alkyle inférieur ou trifluorométhyle; R_3' représente un atome d'hydrogène ou un groupe alkyle inférieur; et leurs sels pharmaceutiquement acceptables.

17. Composés selon la revendication 15, de formule V, dans lesquels R_1' et R_3' représentent des atomes d'hydrogène; R_2' représente le groupe 3-pyridyle, p-cyanobenzyle ou p-cyanophényle; et leurs sels pharmaceutiquement acceptables.

18. Composés de formule VI



(VI)

dans laquelle R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, phényle, (alkyl inférieur)-thio, phényl-(alkyl inférieur)-thio, phénylthio, pyridyle, thiényle, benzyle; ou R_2' représente un radical phényle, phényl-(alkyl inférieur)-thio, phénylthio ou benzyle, chacun monosubstitué sur le noyau phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, benzoyloxy, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; ou R_1' et R_2' réunis représentent ensemble un groupe alkylidène inférieur, benzylidène ou diphénylméthylidène; ou R_1' et R_2' réunis représentent ensemble un groupe alkylène à chaîne droite en C_4-C_6; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; et sels pharmaceutiquement acceptables de ceux-ci.

19. Composés selon les revendications 4 et 18, de formule VI, dans lesquels R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur ou pyridyle; ou R_2' représente un radical benzyle ou phényle chacun non substitué ou monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; et sels pharmaceutiquement acceptables de ceux-ci.

20. Composés selon la revendication 19, de formule VI, dans lesquels R_1' et R_3 représentent des atomes d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, benzyle, phényle ou 3- ou 4-pyridyle; ou R_2' représente un radical phényle ou benzyle substitués chacun sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alcoxy inférieur, alkyle inférieur ou trifluorométhyle; et sels pharmaceutiquement acceptables de ceux-ci.

21. Composés selon la revendication 19, de formule VI, dans lesquels R_1' et R_3 représentent un atome d'hydrogène; R_2' représente le groupe 3- ou 4-pyridyle, p-cyanobenzyle ou p-cyanophényle; et sels pharmaceutiquement acceptables de ceux-ci.

22. Composé selon la revendication 4, qui est le 4-(α-isopropyl-1-imidazolylméthyl)-benzonitrile, un stéréoisomère ou un mélange de stéréoisomères de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci.

23. Composé selon la revendication 4, qui est le 4-[α-(3-pyridyl)-1-imidazolylméthyl]-benzonitrile, un stéréoisomère ou un mélange de stéréoisomères de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci.

24. Composé selon la revendication 4, qui est le 4-[α-(4-cyanophényl)-1-imidazolylméthyl]-benzonitrile ou un sel pharmaceutiquement acceptable de celui-ci.

25. Composé selon la revendication 4, qui est le 4-(α-benzyl-1-imidazolylméthyl)-benzonitrile, un stéréoisomère ou un mélange de stéréoisomères de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci.

26. Composé selon la revendication 4, qui est le 2-(4-cyanophényl)-2-(1-imidazolyl)-indane, ou un sel pharmaceutiquement acceptable de celui-ci.

27. Composé selon la revendication 4, qui est le 4-[α-(4-cyanophényl)-1-(1,2,4-triazolyl)méthyl]-benzonitrile, ou un sel pharmaceutiquement acceptable de celui-ci.

28. Compositions pharmaceutiques comprenant un composé selon l'une quelconque des revendications 4 à 27, conjointement avec un véhicule pharmaceutiquement acceptable.

29. Composé selon l'une quelconque des revendications 4 à 27 pour utilisation dans un procédé de traitement thérapeutique de l'organisme animal ou humain.

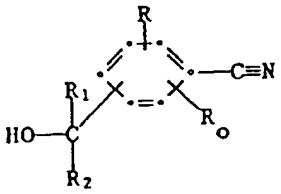
30. Utilisation d'un composé selon l'une quelconque des revendications 4 à 27, pour la préparation d'une composition pharmaceutique pour le traitement d'états répondant à des inhibiteurs de l'activité aromatase.

31. Procédé pour la préparation des composés de formule I selon la revendication 1, ou de leurs sels, comprenant

a) pour les composés de formule I dans lesquels W représente un radical 1-imidazolyle ou 1-triazolyle éventuellement substitués chacun par un groupe alkyle inférieur, la condensation d'un composé de formule VII

W'-H (VII)

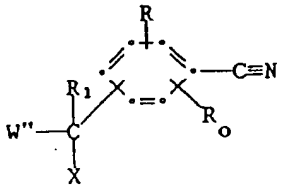
dans laquelle W' représente un radical 1-imidazolyle ou 1-triazolyle chacun éventuellement substitué par un groupe alkyle inférieur, ou l'un de ses dérivés protégés à l'azote, avec un dérivé estérifié réactif d'un composé de formule VIII



(VIII)

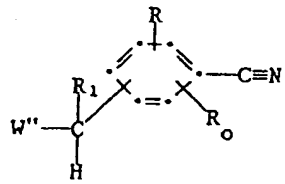
dans laquelle R, R_0, R_1 et R_2 ont les mêmes significations que celles données ici à propos de la formule I;

b) pour les composés dans lesquels W représente un radical 3-pyridyle éventuellement substitué par un groupe alkyle inférieur, la déshalogénation d'un composé de formule IX



(IX)

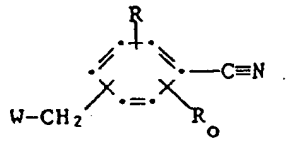
dans laquelle W" représente un radical 3-pyridyle éventuellement substitué par un groupe alkyle inférieur, X représente un atome d'halogène, de préférence de chlore, R et R_0 ont les mêmes significations que celles données ici pour les composés de formule I, et R_1 a la même signification que celle donnée ici à propos de la formule I, et, si nécessaire, la mise en réaction du produit de formule X résultant



(X)

avec un dérivé réactif du radical R_2, en utilisant le processus c) ci-dessous;

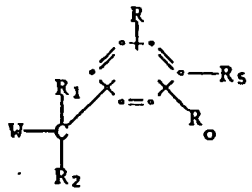
c) la condensation, dans des conditions basiques, d'un composé de formule XI



(XI)

(qui est un composé de formule I dans lequel R_1 et R_2 représentent des atomes d'hydrogène) dans laquelle R, R_0 et W ont les mêmes significations que celles données ici pour la formule I,
avec un dérivé fonctionnel réactif d'un radical R_1 ou R_2 (R_1 ou R_2 ne représentant pas un atome d'hydrogène) pour obtenir un composé de formule I dans lequel un seul des radicaux R_1 et R_2 représente un atome d'hydrogène; ou de même, la condensation d'une composé de formule I ainsi obtenu avec un dérivé fonctionnel réactif d'un radical R_1 ou R_2 (R_1 ou R_2 ne représentant pas un atome d'hydrogène) pour obtenir un composé de formule I dans lequel ni R_1 ni R_2 ne représentent un atome d'hydrogène; ou la condensation d'un composé de formule XI avec un dérivé bifonctionnel réactif de R_1 et R_2 réunis représentant un groupe alkylène à chaîne droite en C_4-C_6, un groupe alkylène à chaîne droite en C_4-C_6 substitué par un groupe alkyle inférieur, ou un groupe alkylène à chaine droite en C_2-C_4 pontée par un radical 1,2-phénylène, pour obtenir un composé correspondant de formule I;

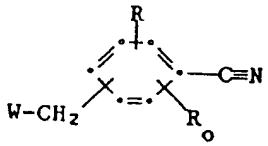
d) la conversion de R_5 en groupe cyano dans un composé de formule XII



(XII)

dans laquelle W, R, R_0, R_1 et R_2 ont les mêmes significations que celles données plus haut, et R_5 représente un groupe ou radical qui peut être converti en le groupe cyano;
et/ou la conversion d'un composé de formulé I en un autre composé de formule I; et/ou la conversion d'un composé libre en un sel, et/ou la conversion d'un sel en un composé libre ou en un autre sel; et/ou la séparation d'un mélange d'isomères ou de racémiques en les isomères ou racémiques individuels et/ou la résolution d'un racémique en les isomères optiques.

32. Procédé selon la revendication 31, pour la préparation d'un composé de formule I dans lequel R_1 représente un atome d'hydrogène; R_2 représente le groupe 4-cyanophényle; W, R, R_0 ont les mêmes significations que celles données dans ladite revendication; comprenant la condensation, dans des conditions basiques, d'un composé de formule XI



(XI)

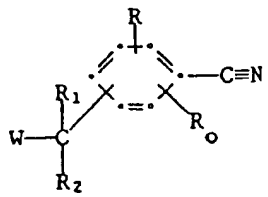
avec le p-fluorobenzonitrile.

33. Procédé selon la revendication 32, pour la préparation du 4-[α-(4-cyanophényl)-1-imidazolylméthyl]-benzonitrile.

34. Procédé selon la revendication 32, pour la préparation du 4-[α-(4-cyanophényl)-1-(1,2,4-triazolyl)-méthyl]-benzonitrile.

Revendications pour les Etats contractants suivants : AT, ES, GR

1. Procédé pour la préparation d'un composé de formule I



(I)

dans laquelle R et R_0 représentent indépendamment un atome d'hydrogène ou un groupe alkyle inférieur; ou R et R_0, situés sur des atomes de carbone adjacents, forment ensemble, conjointement avec le cycle benzénique auquel ils sont liés, un cycle naphtalène ou tétrahydronaphtalène; R_1 représente un atome d'hydrogène; R_2 représente un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur, aryle, aryl-alkyle inférieur, cycloalkyle en C_3-C_6 ou cycloalkyl(C_3-C_6)- alkyle inférieur; ou R_1 et R_2 réunis représentent ensemble un groupe alkylidène inférieur ou mono- ou diaryl-alkylidène inférieur; R_1 et R_2 réunis représentent également un groupe alkylène à chaîne droite en C_4-C_6, alkylène à chaîne droite substitué par un groupe alkyle inférieur ou alkylène à chaîne droite en C_2-C_4 pontée par un groupe o-phénylène, pour former, avec l'atome de carbone auquel ils sont liés, un cycle

à 5, 6 ou 7 chaînons correspondant, éventuellement substitué ou soudé à un noyau benzénique; W représente le groupe 1-imidazolyle, 1-(1,2,4-ou -1,3,4)-triazolyle ou 3-pyridyle; ou W représente un groupe 1-imidazolyle, 1-(1,2,4- ou -1,3,4)-triazolyle ou 3-pyridyle substitué par un radical alkyle inférieur;

et "aryle" dans les définitions ci-dessus représente un groupe phényle qui est non substitué ou substitué par un ou deux substituants choisis parmi des atomes d'halogène et des groupes alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, aroyloxy, (alcoxy inférieur)-carbonyloxy, N,N-di(alkyl inférieur)-carbamoyloxy, nitro, amino, trifluorométhyle, cyano, carboxy, (alcoxy inférieur)-carbonyle, (phényl, naphtyl, pyridyl, thiényl, indolyl ou furyl)-(alcoxy inférieur)-carbonyle, alcanoyloxy inférieur(alcoxy inférieur)-carbonyle, 3-phtalidoxycarbonyle, carbamoyle, N-(alkyl inférieur)-carbamoyle, N,N-di(alkyl inférieur)-carbamoyle, alcanoyle inférieur, aroyle, (alkyl inférieur)-sulfonyle, sulfamoyle, N-(alkyl inférieur)-sulfamoyle et N,N-di(alkyl inférieur)-sulfamoyle; un groupe 1- ou 2-naphtyle qui est non substitué ou substitué par des substituants halogène, alkyle inférieur, alcoxy inférieur ou cyano; un radical aromatique hétérocyclique choisi parmi les radicaux thiényle, indolyle, pyridyle et furyle; ou un tel radical aromatique hétérocyclique qui est monosubstitué par un atome d'halogène ou par un groupe alkyle inférieur, alcoxy inférieur ou cyano;

et "aroyle" dans les définitions ci-dessus représente un radical benzoyle qui est non substitué ou substitué par 1 ou 2 atomes d'halogène ou groupes alkyle inférieur, alcoxy inférieur ou trifluorométhyle; le radical thiénoyle, pyrroloyle ou 2-, 3- ou 4-pyridylcarbonyle;

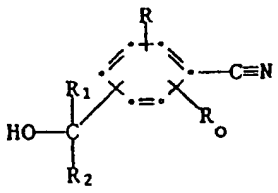
et les radicaux désignés comme "inférieurs" contiennent jusqu'à et y compris 7 atomes de carbone;

ou d'un sel pharmaceutiquement acceptable de celui-ci, comprenant

a) pour les composés de formule I dans lesquels W représente un radical 1-imidazolyle ou 1-triazolyle éventuellement substitués chacun par un groupe alkyle inférieur, la condensation d'un composé de formule VII

W'-H (VII)

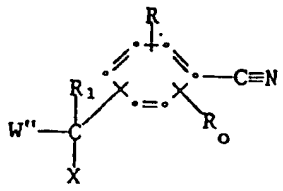
dans laquelle W' représente un radical 1-imidazolyle ou 1-triazolyle chacun éventuellement substitué par un groupe alkyle inférieur, ou l'un de ses dérivés protégés à l'azote, avec un dérivé estérifié réactif d'un composé de formule VIII



(VIII)

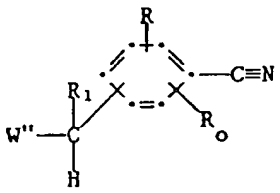
dans laquelle R, R_0, R_1 et R_2 ont les mêmes significations que celles données ici à propos de la formule I;

b) pour les composés dans lesquels W représente un radical 3-pyridyle éventuellement substitué par un groupe alkyle inférieur, la déshalogénation d'un composé de formule IX



(IX)

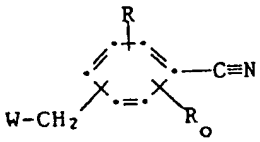
dans laquelle W" représente un radical 3-pyridyle éventuellement substitué par un groupe alkyle inférieur, X représente un atome d'halogène, de préférence de chlore, R et R_0 ont les mêmes significations que celles données ici pour les composés de formule I, et R_1 a la même signification que celle donnée ici à propos de la formule I, et, si nécessaire, la mise en réaction du produit de formule X résultant



(X)

avec un dérivé réactif du radical R_2, en utilisant le processus c) ci-dessous;

c) la condensation, dans des conditions basiques, d'un composé de formule XI

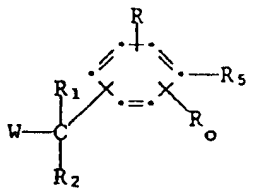


(XI)

(qui est un composé de formule I dans lequel R_1 et R_2 représentent des atomes d'hydrogène) dans laquelle R, R_0 et W ont les mêmes significations que celles données ici pour la formule I,

avec un dérivé fonctionnel réactif d'un radical R_1 ou R_2 (R_1 ou R_2 ne représentant pas un atome d'hydrogène) pour obtenir un composé de formule I dans lequel un seul des radicaux R_1 et R_2 représente un atome d'hydrogène; ou de même, la condensation d'une composé de formule I ainsi obtenu avec un dérivé fonctionnel réactif d'un radical R_1 ou R_2 (R_1 ou R_2 ne représentant pas un atome d'hydrogène) pour obtenir un composé de formule I dans lequel ni R_1 ni R_2 ne représentent un atome d'hydrogène; ou la condensation d'un composé de formule XI avec un dérivé bifonctionnel réactif de R_1 et R_2 réunis représentant un groupe alkylène à chaîne droite en C_4-C_6, un groupe alkylène à chaîne droite en C_4-C_6 substitué par un groupe alkyle inférieur, ou un groupe alkylène à chaîne droite en C_2-C_4 pontée par un radical 1,2-phénylène, pour obtenir un composé correspondant de formule I;

d) la conversion de R_5 en groupe cyano dans un composé de formule XII

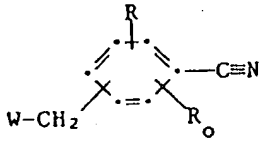


(XII)

dans laquelle W, R, R_0, R_1 et R_2 ont les mêmes significations que celles données plus haut, et R_5 représente un groupe ou radical qui peut être converti en le groupe cyano;

et/ou la conversion d'un composé de formule I en un autre composé de formule I; et/ou la conversion d'un composé libre en un sel, et/ou la conversion d'un sel en un composé libre ou en un autre sel; et/ou la séparation d'un mélange d'isomères ou de racémiques en les isomères ou racémiques individuels et/ou la résolution d'un racémique en les isomères optiques.

2. Procédé selon la revendication 1, pour la préparation d'un composé de formule I dans lequel R_1 représente un atome d'hydrogène; R_2 représente le groupe 4-cyanophényle; W, R, R_0 ont les mêmes significations que celles données dans ladite revendication; comprenant la condensation, dans des conditions basiques, d'un composé de formule XI



(XI)

avec le p-fluorobenzonitrile.

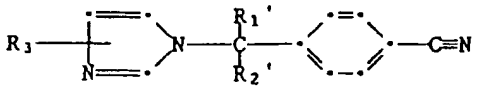
3. Procédé selon la revendication 2, pour la préparation du 4-[α-(4-cyanophényl)-1-imidazolylméthyl]-benzonitrile.

4. Procédé selon la revendication 2, pour la préparation du 4-[α-(4-cyanophényl)-1-(1,2,4-triazolyl)méthyl]-benzonitrile.

5. Procédé selon la revendication 1, pour la préparation d'un composé de formule I, dans lequel R et R_0 représentent un atome d'hydrogène; ou R et R_0, situés sur des atomes de carbone adjacents, forment ensemble, conjointement avec le noyau benzénique auquel ils sont liés, un cycle naphtalène; R_1 représente un atome d'hydrogène; R_2 représente un atome d'hydrogène ou un groupe alkyle inferieur, aryle ou aryl-alkyle inférieur; ou R_1 et R_2 réunis représentent ensemble un groupe alkylidène inférieur ou diaryl-alkylidène inférieur; R_1 et R_2 réunis peuvent également représenter un groupe alkylène à chaîne droite en C_4-C_6 ou alkylène à chaîne droite en C_2-C_4 pontée par un radical o-phénylène, pour former, avec l'atome de carbone auquel ils sont liés, un cycle à 5, 6 ou 7 chaînons correspondant, éventuellement soudé à un noyau bénzénique; W représente le groupe 1-imidazoyle, 1-(1,2,4- ou -1,3,4)-triazolyle, 3-pyridyle ou un groupe 1-imidazolyle substitué par un groupe alkyle inférieur; et "aryle" dans les définitions ci-dessus représente le radical phényle ou un radical phényle substitué par un atome d'halogène et par un groupe alkyle inférieur, alcoxy inférieur, hydroxy, trifluorométhyle ou cyano; le radical thiényle ou pyridyle; ou d'un sel pharmaceutiquement acceptable de celui-ci.

6. Procédé selon la revendication 1, pour la préparation d'un composé de formule I, dans lequel R et R_0 représentent indépendamment un atome d'hydrogène ou un groupe alkyle inférieur; ou R et R_0, situés sur des atomes de carbone adjacents, forment ensemble, conjointement avec le noyau benzénique auquel ils sont liés, un cycle naphtalène ou tétrahydronaphtalène; R_1 représente un atome d'hydrogène; R_2 représente un atome d'hydrogène ou un groupe alkyle inférieur, alcényle inférieur, aryle ou aryl-alkyle inférieur; ou R_1 et R_2 représentent ensemble un groupe alkylidène inférieur ou alkylène en C_4-C_6; W représente le groupe 1-imidazolyle ou un groupe 1-imidazolyle substitué par un radical alkyle inférieur; et "aryle" dans les définitions ci-dessus représente le groupe phényle ou un groupe phényle substitué par un ou deux substituants choisis parmi des atomes d'halogène et des groupes alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, nitro, amino, trifluorométhyle, cyano, carboxy, (alcoxy inférieur)-carbonyle, carbamoyle, N-(alkyl inférieur)-carbamoyle, N,N-di(alkyl inférieur)-carbamoyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, sulfamoyle, N-(alkyl inférieur)-sulfamoyle ou N,N-di(alkyl inférieur)-sulfamoyle; ou "aryle" dans les définitions ci-dessus représente également un radical aromatique hétérocyclique choisi parmi les radicaux thiényle, indolyle, pyridyle et furyle; ou un tel radical hétérocyclique monosubstitué par un atome d'halogène ou un groupe alkyle inférieur, alcoxy inférieur ou cyano; ou d'un sel pharmaceutiquement acceptable de celui-ci.

7. Procédé selon la revendication 1, pour la préparation d'un composé de formule II



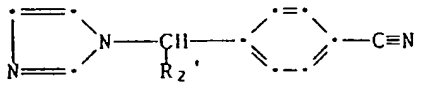
(II)

dans laquelle R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, phényle, pyridyle, thiényle ou benzyle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, benzoyloxy, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; ou R_1' et R_2' réunis représentent ensemble un groupe alkylidène inférieur, benzylidène ou diphénylméthylidène; ou R_1' et R_2' réunis représentent ensemble un groupe alkylène à chaîne droite en C_4-C_6; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; ou d'un sel pharmaceutiquement acceptable de celui-ci.

8. Procédé selon la revendication 7, pour la préparation d'un composé de de formule II, dans lequel R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, pyridyle, benzyle ou phényle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; ou d'un sel pharmaceutiquement acceptable de celui-ci.

9. Procédé selon la revendication 7, pour la préparation d'un composé de formule II, dans lequel R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, benzyle, phényle ou 3-ou 4-pyridyle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alcoxy inférieur, alkyle inférieur ou trifluorométhyle; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur en position 4 ou 5; ou d'un sel pharmaceutiquement acceptable de celui-ci.

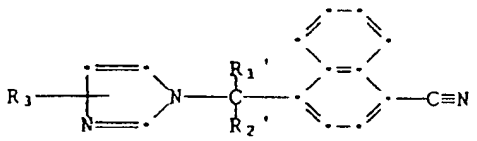
10. Procédé selon la revendication 1, pour la préparation d'un composé de de formule III



(I.I)

dans laquelle R_2' représente le groupe 3-pyridyle, p-cyanobenzyle ou p-cyanophényle; ou d'un sel pharmaceutiquement acceptable de celui-ci.

11. Procédé pour la préparation d'un composé de formule IV



(IV)

dans laquelle R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, phényle, (alkyl inférieur)-thio, phényl-(alkyl inférieur)-thio, phénylthio, pyridyle, thiényle ou benzyle; ou R_2' représente un radical phényle, phényl-(alkyl inférieur)thio, phénylthio ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, benzoyloxy, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; ou R_1' et R_2' réunis représentent ensemble un groupe alkylidène inférieur, benzylidène, diphénylméthylidène; ou R_1' et R_2' réunis représentent ensemble un groupe alkylène à chaine droite en C_4-C_6; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; ou d'un sel pharmaceutiquement acceptable de celui-ci, ledit procédé étant effectué selon l'un quelconque des processus a), c) ou d) mentionnés dans la revendication 1, avec utilisation des produits de départ qui portent les substituants appropriés pour l'obtention des composés de formule IV, et/ou conversion d'un composé de formule IV en un autre composé de formule IV, et/ou conversion d'un composé libre en un sel, et/ou conversion d'un sel en un composé libre ou en un autre sel, et/ou séparation d'un mélange d'isomères ou de racémiques en les isomères ou racémiques individuels, et/ou résolution d'un racémique en les isomères optiques.

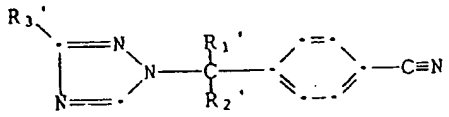
12. Procédé selon la revendication 11, pour la préparation d'un composé de formule IV, dans lequel R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur ou pyridyle; ou R_2' représente un groupe benzyle ou phényle, chacun non substitué ou monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; R_3 représente un atome d'hydrogène ou un groupe alkyle

inférieur; ou d'un sel pharmaceutiquement acceptable de celui-ci.

13. Procédé selon la revendication 12, pour la préparation d'un composé de formule IV, dans lequel R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, benzyle, phényle ou 3- ou 4-pyridyle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alcoxy inférieur, alkyle inférieur ou trifluorométhyle; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur en position 4 ou 5; ou d'un sel pharmaceutiquement acceptable de celui-ci.

14. Procédé selon la revendication 12, pour la préparation d'un composé de formule IV, dans lequel R_1' et R_3 représentent un atome d'hydrogène; R_2' représente le groupe 3-pyridyle, p-cyanobenzyle ou p-cyanophényle; ou d'un sel pharmaceutiquement acceptable de celui-ci.

15. Procédé selon la revendication 1, pour la préparation d'un composé de formule V



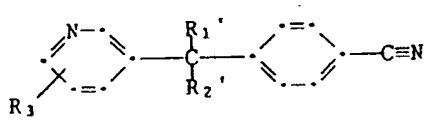
(V)

dans laquelle R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, phényle, pyridyle, thiényle ou benzyle ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le noyau phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, benzoyloxy, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; ou R_1' et R_2' réunis représentent ensemble un groupe alkylidène inférieur, benzylidène ou diphénylméthylidène; ou R_1' et R_2' réunis représentent ensemble un groupe alkylène à chaine droite en C_4-C_6; R_3' représente un atome d'hydrogène ou un groupe alkyle inférieur; ou d'un sel pharmaceutiquement acceptable de celui-ci.

16. Procédé selon la revendication 15, pour la préparation d'un composé de formule V, dans lequel R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, benzyle, phényle ou 3- ou 4-pyridyle; ou R_2' représente un radical phényle ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou un groupe cyano, alcoxy inférieur, alkyle inférieur ou trifluorométhyle; R_3' représente un atome d'hydrogène ou un groupe alkyle inférieur; ou d'un sel pharmaceutiquement acceptable de celui-ci.

17. Procédé selon la revendication 15, pour la préparation d'un composé de formule V, dans lequel R_1' et R_3' représentent des atomes d'hydrogène; R_2' représente le groupe 3-pyridyle, p-cyanobenzyle ou p-cyanophényle; ou d'un sel pharmaceutiquement acceptable de celui-ci.

18. Procédé pour la préparation d'un composé de formule IV



(VI)

dans laquelle R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, phényle, (alkyl inférieur)-thio, phényl-(alkyl inférieur)-thio, phénylthio, pyridyle, thiényle ou benzyle; ou R_2' représente un radical phényle, phényl-(alkyl inférieur)thio, phénylthio ou benzyle, chacun monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, benzoyloxy, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; ou R_1' et R_2' réunis

représentent ensemble un groupe alkylidène inférieur, benzylidène, diphénylméthylidène; ou R_1' et R_2' réunis représentent ensemble un groupe alkylène à chaîne droite en C_4-C_5; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; ou d'un sel pharmaceutiquement acceptable de celui-ci, ledit procédé étant effectué selon l'un quelconque des processus a), b), c) ou d) mentionnés dans la revendication 1, avec utilisation des produits de départ qui portent des substituants appropriés pour l'obtention des composés de formule IV, et/ou conversion d'un composé de formule IV en un autre composé de formule IV, et/ou conversion d'un composé libre en un sel, et/ou conversion d'un sel en un composé libre ou en un autre sel, et/ou séparation d'un mélange d'isomères ou de racémiques en les isomères ou racémiques individuels, et/ou résolution d'un racémique en les isomères optiques.

19. Procédé selon la revendication 18, pour la préparation d'un composé de formule VI, dans lequel R_1' représente un atome d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur ou pyridyle; ou R_2' représente un radical benzyle ou phényle chacun non substitué ou monosubstitué sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alkyle inférieur, alcoxy inférieur, hydroxy, alcanoyloxy inférieur, nitro, trifluorométhyle, alcanoyle inférieur, benzoyle, (alkyl inférieur)-sulfonyle, carbamoyle, N-mono- ou N,N-di(alkyl inférieur)-carbamoyle, sulfamoyle, N-mono- ou N,N-di(alkyl inférieur)-sulfamoyle; R_3 représente un atome d'hydrogène ou un groupe alkyle inférieur; ou d'un sel pharmaceutiquement acceptable de celui-ci.

20. Procédé selon la revendication 19, pour la préparation d'un composé de formule VI, dans lequel R_1' et R_3 représentent des atomes d'hydrogène; R_2' représente un atome d'hydrogène ou un groupe alkyle inférieur, benzyle, phényle ou 3- ou 4-pyridyle; ou R_2' représente un radical phényle ou benzyle substitués chacun sur le fragment phényle par un atome d'halogène ou par un groupe cyano, alcoxy inférieur, alkyle inférieur ou trifluorométhyle; ou d'un sel pharmaceutiquement acceptable de celui-ci.

21. Procédé selon la revendication 19, pour la préparation d'un composé de formule VI, dans lequel R_1' et R_3 représentent un atome d'hydrogène; R_2' représente le groupe 3- ou 4-pyridyle, p-cyanobenzyle ou p-cyanophényle; ou d'un sel pharmaceutiquement acceptable de celui-ci.

22. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 4-(α-isopropyl-1-imidazolylméthyl)-benzonitrile, un stéréoisomère ou un mélange de stéréoisomères de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci.

23. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 4-[α-(3-pyridyl)-1-imidazolylméthyl]-benzonitrile, un stéréoisomère ou un mélange de stéréoisomères de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci.

24. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 4-[α-(4-cyanophényl)-1-imidazolylméthyl]-benzonitrile ou un sel pharmaceutiquement acceptable de celui-ci.

25. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 4-(α-benzyl-1-imidazolylméthyl)-benzonitrile, un stéréoisomère ou un mélange de stéréoisomères de celui-ci, ou un sel pharmaceutiquement acceptable de celui-ci.

26. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 2-(4-cyanophényl)-2-(1-imidazolyl)-indane, ou un sel pharmaceutiquement acceptable de celui-ci.

27. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 4-[α-(4-cyanophényl)-1-(1,2,4-triazolyl)méthyl]-benzonitrile, ou un sel pharmaceutiquement acceptable de celui-ci.

28. Procédé pour la préparation d'un composition pharmaceutique, comprenant l'incorporation d'un compose pouvant être obtenu selon l'une quelconque des revendications 1 à 27, dans lesdites préparations, à un pourcentage de 1-50 %.